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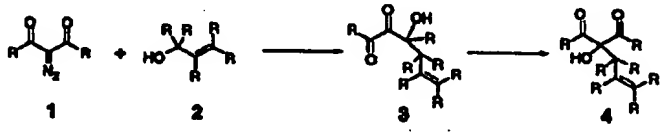
(54) Title: GLYCOSYLATED INDOLOCARBAZOLE SYNTHESIS

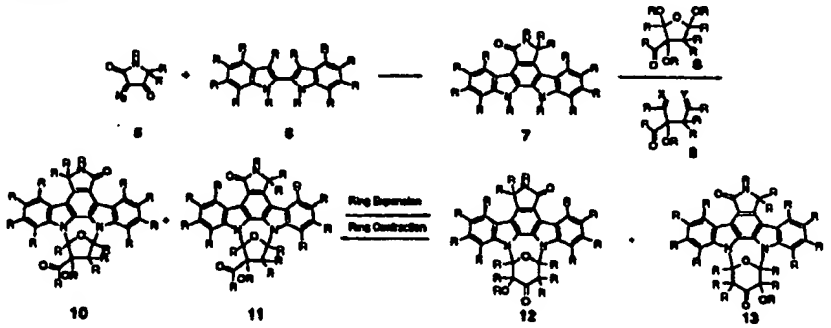
(57) Abstract

Tertiary alcohols containing the structural features illustrated in 3 or 4 (Scheme I) are prepared by reacting at least one diazo carbonyl compound, (e.g., 1 in Scheme I) and at least one allylic alcohol (e.g., 2 in Scheme I) in a coupling reaction run under conditions that produce carbene or carbenoid intermediates from the diazo-containing substrate such as transition metal catalysis or either thermal or photochemical decomposition. In some preferred embodiments, $Rh_2(OAc)_4$ is employed to catalyze the coupling reaction. In Scheme I R represents a substituent comprised of any number and combination of the elements H, C, N, S, Si, O, Cl, Br, I, and F. Indolocarbazoles (e.g., 7 in Scheme II) are prepared by coupling of diazo carbonyl compounds (e.g., 5 Scheme II) and biindoles (e.g., 6 in Scheme II). Indolocarbazoles are furanosylated (e.g., 7 in Scheme II) with acetals (e.g., 8 in Scheme II) or their open chain congeners (e.g., 9 in Scheme II) under conditions known to promote acetal exchange or formation, such as protic or Lewis acids. Furanosylated indolocarbazoles (e.g., 10 in Scheme II) are also prepared via ring contraction of pyranosylated indolocarbazoles (e.g., 11 in Scheme II) under conditions know to effect oxidation and benzylic acid type rearrangements, and pyranosylated indolocarbazoles (e.g., 11 in Scheme II) are prepared via ring expansion of the furanosylated congeners (e.g., 10 in Scheme II).

Scheme I



Scheme II



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GLYCOSYLATED INDOLOCARBAZOLE SYNTHESIS

Relat d Application Data

This is a continuation-in-part of U.S. provisional application serial number 60/002,164 filed August 11, 1995, which is incorporated herein by reference.

Technical Field

This invention relates to the synthesis of tertiary alcohols by coupling of diazo carbonyl compounds with allylic alcohols under conditions that produce carbene or carbenoid intermediates. Both furanosylated and pyranosylated indolocarbazoles are prepared, including naturally occurring compounds as well as a range of structurally diverse analogues.

Background of the Invention

Originally discovered in the course of screening for microbial alkaloids, staurosporine and structurally related compounds have been the object of considerable investigation for various biomedical purposes for the past twenty years (for a review, see Omura, *et al.*). It has been recently reported that staurosporine and its derivatives, for example, inhibit smooth muscle contraction, platelet aggregation, neurotrophic activity, and, most importantly, protein kinases *in vitro* and *in vivo* (*ibid.*).

Disruption of cellular signal transduction via kinase malfunction has been related to the onset of several disease states, including rhematoid arthritis, systemic lupus erythematosis, diabetes metillus and Alzheimer's disease. For example, the clinical severity of Alzheimer's disease correlates well with the formation of amyloid plaques and neurofibrillary tangles; both manifest paired helical filaments (PHF) that possess an overphosphorylated microtubule associated protein (M.A.P., also known as τ-protein). It has be n suggested that overphosphorylation may lead to

conformational changes that inhibit τ binding to microtubules. Recently, a bovine τ-kinase denominated PK40 (molecular weight 40,000) has been isolated and shown to induce a gel mobility shift of PHF-τ. PK40 is not closely associated with the cytoskeleton and appears to be a member of the extracellular regulated kinases. Specific inhibition of enzymes like PK40 by small, orally bioavailable compounds, promise to be a highly successful means of treating Alzheimer's disease.

Unfortunately, the structural homology shared by the many kinase isozymes has impeded the development of selective and therapeutically useful inhibitors. It would be desirable to have others.

Summary of the Invention

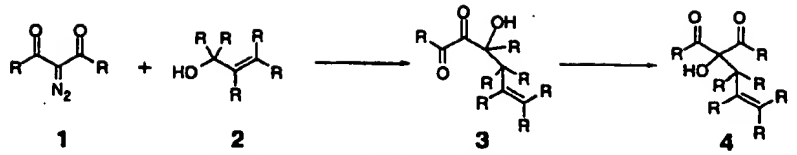
It is a specific object of the invention to provide a synthesis for (+)- and (-)- K252a, analogues of K252a, staurosporine and its congeners, and the like.

It is another and more general object of the invention to provide for the synthesis of furanosylated and pyranosylated indolocarbzoles, particularly the interconversion of furanosylated indolocarbazoles to the corresponding pyranosylated derivatives.

It is a further object of the invention to provide an efficient approach to the synthesis of enantioenriched tertiary alcohols.

These and other objects are accomplished by the present invention, which provides a process for the preparation of tertiary alcohols containing the structural features illustrated in **3** or **4** below (Scheme I). The process utilizes at least one carbonyl compound, *e.g.*, **1** in Scheme I) and at least one allylic alcohol (*e.g.*, **2** in Scheme I) in a coupling reaction that is run under conditions that produce carbene or carbenoid intermediates from the diazo-containing substrate. These conditions include transition metal catalysis or either thermal or photochemical decomposition. In some preferred embodiments illustrated hereafter, $Rh_2(OAc)_4$ is employed to catalyze the coupling reaction.

Schem I

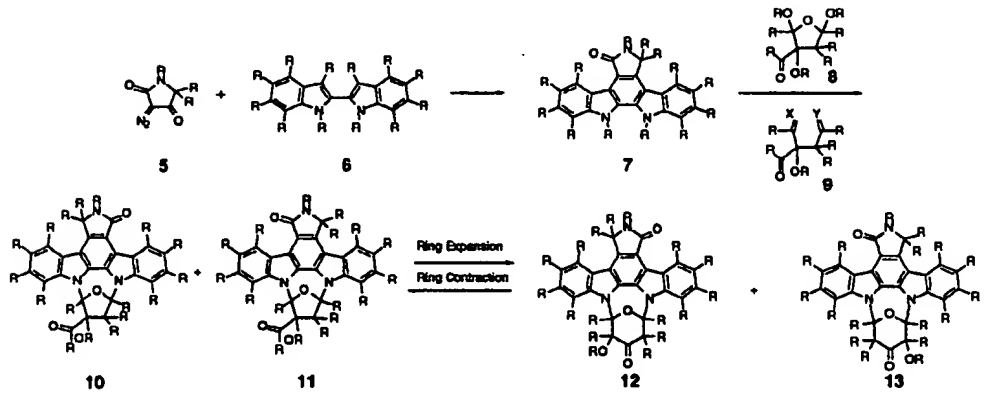


1 2 3 4

Wherein R represents a substituent comprised of any number and combination of the elements H, C, N, S,Si, O, Cl, Br, I, and F

The invention more specifically provides a process for the construction of indolocarbazoles (*e.g.*, **7** below) from the coupling of diazo carbonyl compounds (*e.g.*, **5**) and biindoles (*e.g.*, **6**). The invention also provides a process for the stereoselective preparation of glycosylated indolocarbazoles like but not limited to **10** and **11** via furanosylation of indolocarbozoles (*e.g.*, **7**) with acetals (*e.g.*, **8**) or their open chain congeners (*e.g.*, **9**) under conditions known to promote acetal exchange or formation, such as protic or Lewis acids.

Scheme II



5 6 7 8 9

10 11 12 13

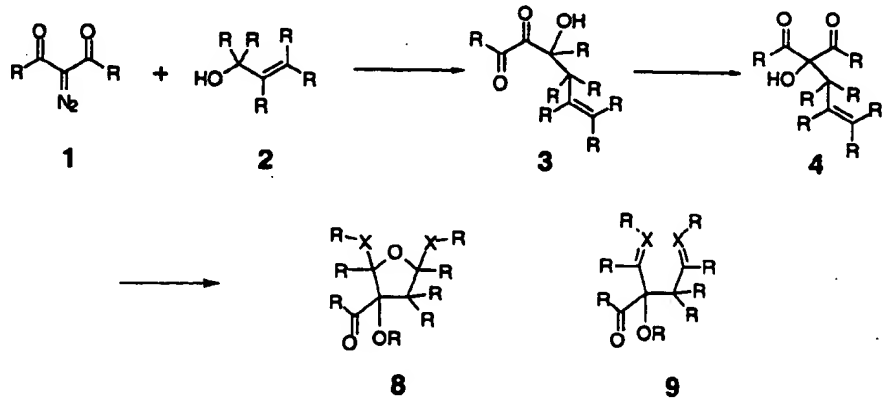
As illustrated in Scheme II above, processes of the invention also provide furanosylated indolocarbazoles (*e.g.*, **10**) via ring contraction of pyranosylated indolocarbazoles (*e.g.*, **12**) under conditions know to effect oxidation and benzylic acid type rearrangements. The invention correspondingly provides processes for the construction of pyranosylated indolocarbazoles (*e.g.*, **12**) via ring expansion of the furanosylated congeners (*e.g.*, **10**).

Detailed Description of the Invention

This invention is based upon several new processes that when combined in-total or in-part can lead to the enantioselective syntheses of various indolocarbazoles.

As summarized above, in a practice of the invention at least one diazo carbonyl compound and at least one allylic alcohol of structures **1** and **2**, respectively (Scheme III), are combined to produce tertiary alcohols of structures **3** and/or **4** in Scheme III. A preferred embodiment employs but is not limited to the use of transition metal catalysts in the form of ligated Rh(II) complexes, for example $Rh_2(OAc)_4$, to produce **3** and a Lewis acid like but not limited to $BF_3 \cdot Et_2O$ to convert **3** to **4**. In alternative embodiments the decomposition of the diazo substrate to the corresponding carbene or carbenoid involves catalysis by complexes of: Cu(II), Mn(II), Fe(II), Co(II), Ni(0), Ni(II), Zn(II), Mo(II), Ru(II), Ru(III), Bronsted and Lewis acids, thermolysis, and/or photolysis. The derived tertiary alcohols of structure **4** are further manipulated by standard chemical procedures to produce acetals of structure **8** and the corresponding open chain congeners of structure **9**. The later are utilized in the furanosylation process and total syntheses described below.

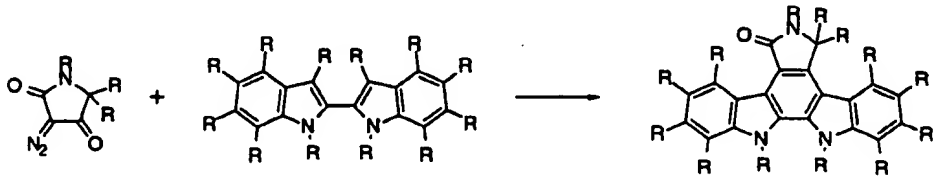
Scheme III



(R represents a substituent comprised of any number and combination of the elements H, C, N, S, Si, O, Cl, Br, I, F)
(X represents a substituent comprised of any number and combination of the elements N, S, Si, O, Cl, Br, I, F)

The invention also provides a process for coupling at least one diazo carbonyl compound and at least one biindole, of structures **5** and **6** respectively (Scheme IV), to produce indolocarbazoles of structure **7**. A preferred embodiment employs but is not limited to the use of transition metal catalysts in the form of ligated Rh(II) complexes, for example $Rh_2(OAc)_4$, in a solvent capable of solvating the substrates such as CH_2Cl_2, pinacolone, and/or CH_3CN. The reaction is carried out under conditions such that products are formed at a convenient rate such as for example about 20-30 minutes at reflux. In alternative embodiments initiating the process via decomposition of the diazo substrate to the corresponding carbene or carbenoid involves catalysis by complexes of: Cu(II), Mn(II), Fe(II), Co(II), Ni(0), Ni(II), Zn(II), Mo(II), Ru(II), Ru(III), Bronsted and Lewis acids, thermolysis, and/or photolysis.

Scheme IV

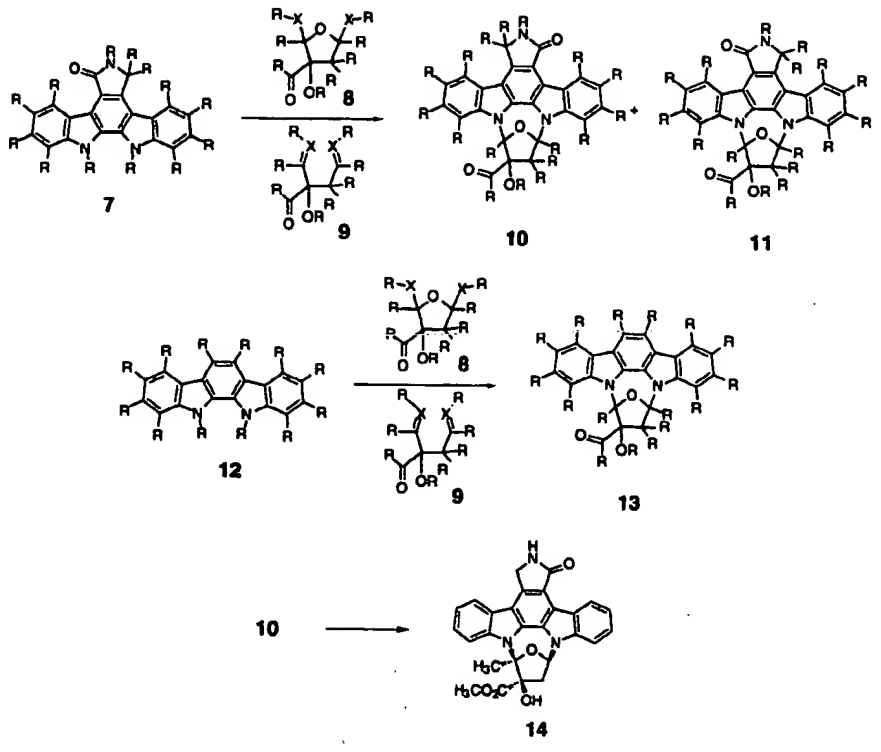


5 **6** **7**

(R represents a substituent comprised of any number and combination of the elements H, C, N, S, Si, O, Cl, Br, I, F)

The invention also provides a process for the stereoselective furanosylation of indolocarbazoles of a structure **10** or **11** with acetals and/or their open chain congeners, of structures **8** and **9** respectively in Scheme V, under conditions that promote acetal exchange or formation, such as but not limited to Bronstead or Lewis acids such as CSA, PTSA, or $BF_3 \cdot Et_2O$ (McCombie *et al.*). A preferred embodiment employs but is not limited to the use of camphor sulfonic acid (CSA) as the catalyst and the dichloroethane as the solvent in a coupling reaction that stereoselectively produces the regioisomeric furanosylated indolocarbazoles **10** and **11** in about 80% yield. The derived indolocarbazoles of structure **10** are manipulated by standard chemical procedures to produce **14** (K252a).

Sch m V

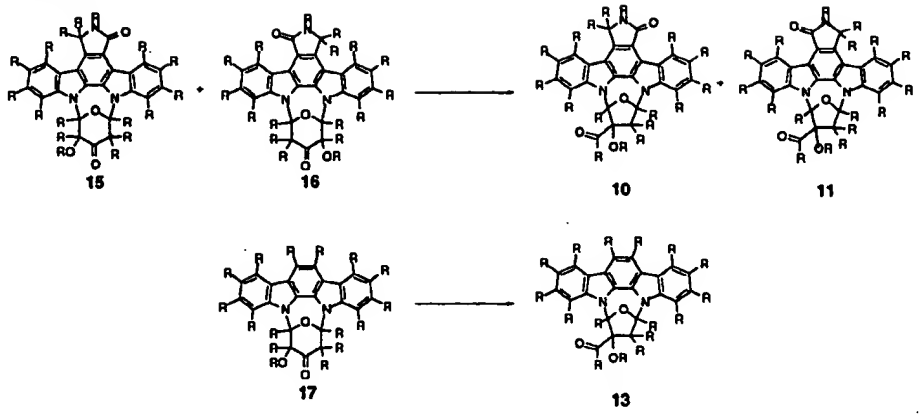


(R represents a substituent comprised of any number and combination of the elements H, C, N, S, Si, O, Cl, Br, I, F)

(X represents a substituent comprised of any number and combination of the elements N, S, Si, O, Cl, Br, I, F)

As illustrated in Scheme VI, the invention also provides a process for the ring contraction of pyranosylated indolocarbazoles of structure **15** and/or **16** to furanosylated indolocarbazoles of structure **10** and/or **11** under conditions that in single- or two-step fashion can effect oxidation and benzylic acid type rearrangement (Fredenhagen *et al.*). A preferred embodiment employs but is not limited to a single-step procedure wherein CuCl is used as both the oxidant and rearrangement promoter and methanol is used as the solvent.

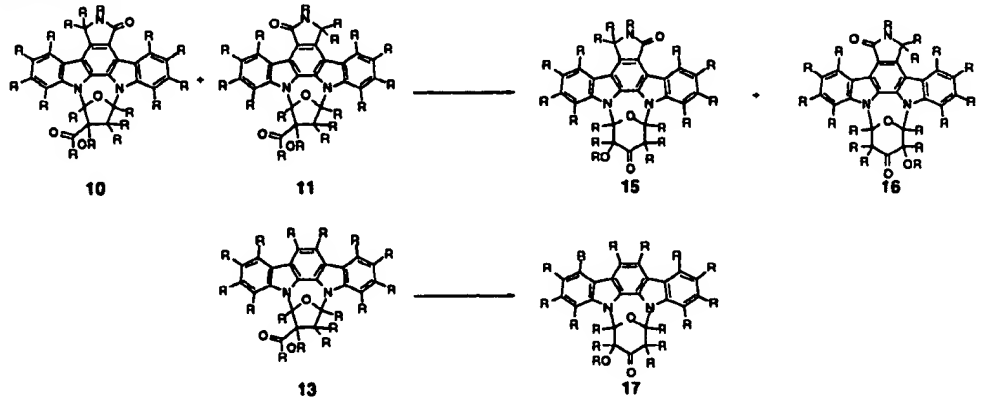
Scheme VI



(R represents a substituent comprised of any number and combination of the elements H, C, N, S, Si, O, Cl, Br, I, F)

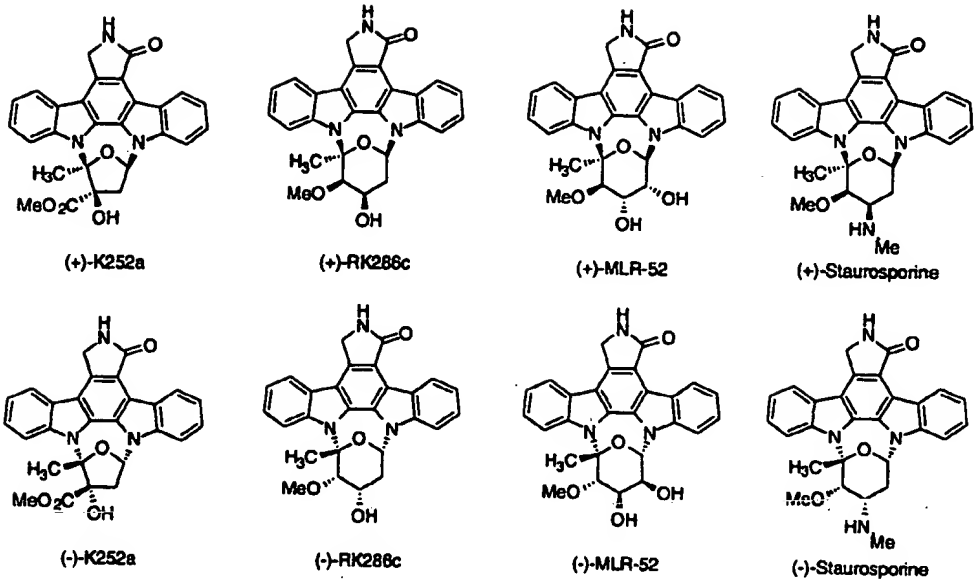
The invention correspondingly provides a process for the ring expansion of furanosylated indolocarbazoles of structure **10** and/or **11** to the pyranosylated congeners of structure **15** and/or **16** illustrated in Scheme VII below (OOtsuka *et al.*). A preferred embodiment employs but is not limited to a multistep procedure wherein **10** and/or **11** is first reduced with $LiBH_4$ and then the derived diol is oxidized. The resulting intermediate compound is then subjected to $BF_3 \cdot Et_2O$ to promote the ring expansion.

Scheme VII



(R represents a substituent comprised of any number and combination of the elements H, C, N, S, Si, O, Cl, Br, I, F)

It is an advantage of the invention that the combined processes provide efficient access to useful indolocarbazoles such as (+)- and (-)-K252a, (+)- and (-)-RK-286c, (+)- and (-)-MLR-52, (+)- and (-)-staurosporine, and the like depicted below.



Examples

The following are presented to further illustrate and explain the present invention and should not be taken as limiting in any regard. Unless otherwise indicated, all parts and percentages are by weight and are based on the weight of the components at the indicated stage of processing. Rotations on indolocarbazole were obtained on methanol solutions. Compound structural assignments were in accord with infrared and high-field ^{1}H (500 MHz) and ^{13}C (125 or 62.5 MHz) NMR spectra, as well as appropriate parent identification by high-resolution mass spectrometry.

Example 1

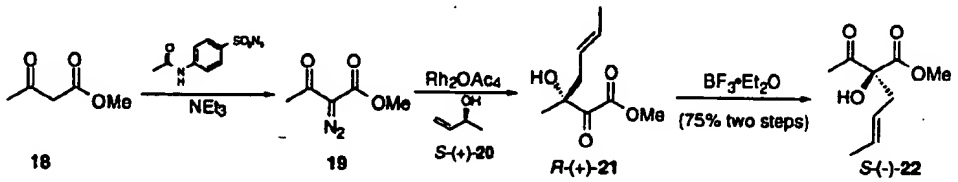
Enantioselective Preparation of Tertiary Alcohols

This example describes a novel rhodium-catalyzed C-C bond forming reaction that allows asymmetric access to **21** (95% ee) and **22** (93% ee) in only two and three steps from methyl acetoacetate (**18**) (Scheme VIII). In this scenario α-keto ester **21** was produced from the rhodium-catalyzed decomposition of **19** in the presence of S-(+)-1-buten-3-ol (**20**) (Wood *et al.*). In the event, complete consumption of **19** was observed after only 20

minutes to reflux in benz ne. Proton NMR analysis of the crude reaction indicated the clean

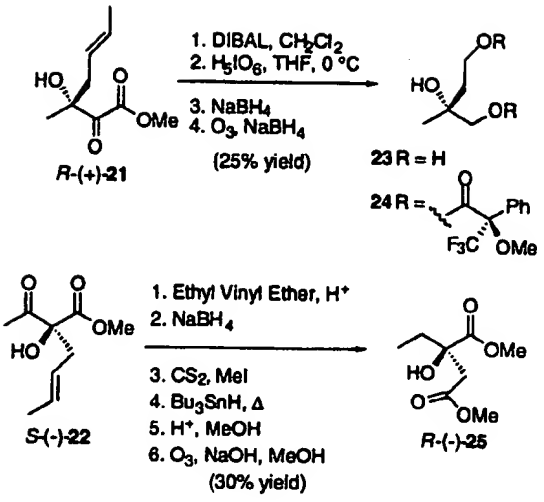
formation of a product similar to **19**; however, the characteristic methyl ketone singlet had shifted from 2.2 to 1.5 ppm. Clearly the allyloxy or allyloxonium ylide intermediate had undergone [3,3] sigmatropic rearrangement to alcohol (+)-**21** (66% yield) (Pirrung *et al.*). Completion of the tandem rearrangement protocol was achieved by exposing (+)-**21** to $BF_3 \cdot Et_2O$ which promoted a clean [1,2]-allyl migration to furnish (-)-**22** in 74% yield. In subsequent studies, improved yields were obtained by conducting the tandem rearrangement in one pot. Thus, introducing an equivalent of $BF_3 \cdot Et_2O$ into the cooled [3,3] reaction allows isolation of (-)-**22** in an overall yield of 75%.

Scheme VIII



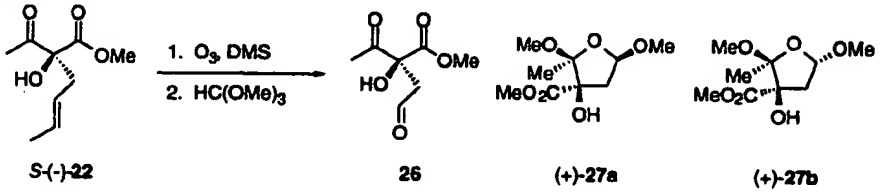
With an approach firmly established, a chemical correlation study was initiated to confirm both the sense and degree of asymmetric induction for the tandem rearrangement. Analysis of the purified products from both the [3,3] (*i.e.*,(+)-**21**) and [1,2] (*i.e.*, (-)-**22**) rearrangements via proton NMR in the presence of $Eu(hfc)_4$ gave the first indication that each step was proceeding with a high degree of stereoselectivity. Conversion of (+)-**21** to **23** as outlined in Scheme IX, followed by comparison of the derived bis Mosher ester (**24**) to samples prepared from *S*-(+)- and *R*-(-)-citramalic acid, established that *S*-(+)-**20** (98% ee) had furnished *R*-(+)-**21** (95% ee). Stereoselectivity in the [1,2] shift was established by degradation of (-)-**22** to R-(-)-**25** followed by DIBAL reduction and proton NMR analysis of the corresponding bis Mosher ester. While the Mosher ester analysis established an ee of 92%, the observation of R-(-)-**25** in the degradation proved th absolute stereochemistry in **22** as *S*.

Scheme IX



Having established the degree and sense of asymmetric induction the asymmetric synthesis of the requisite acetals **26** and **27** was begun. Thus, reductive ozonolysis of **22** followed by acetal formation provided a ternary mixture. Spectral identification of the isolated products indicated the presence of methyl ketone **26** and furanoses (+)-**27a** and (+)-**27b** (Scheme X).

Scheme X



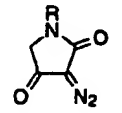
Example 2

Preparation and Furanosylation of Indolocarbazoles
The Synthesis of K252a

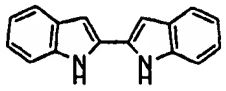
This example describes the coupling of diazolactams **28** and 2,2'-biindole **29** to produce an intermediate that undergoes cycloaromatization to furnish the indolocarbazoles **30**. Application of this strategy allows efficient access to both the parent aglycone (**30a**) and the selectively protected derivatives (**30b-c**). Of the latter, **30c** is employed in the total synthesis of K252a. Overall, preparation of the enantioenriched furanoses **27** (described in Example 1 abov) and aglycon unit **30c** and their

conversion to **14** require only eleven synthetic operations with a longest linear sequence of seven steps.

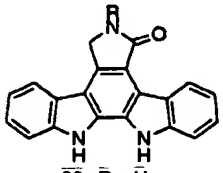
Sch m XI



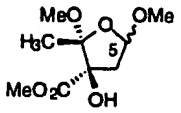
28a R = H
28b R = *t*-Bu
28c R = 3,4-DMB
28d R = PMB
28e R = Bn



29



30a R = H
30b R = *t*-Bu
30c R = 3,4-DMB
30d R = PMB
30e R = Bn

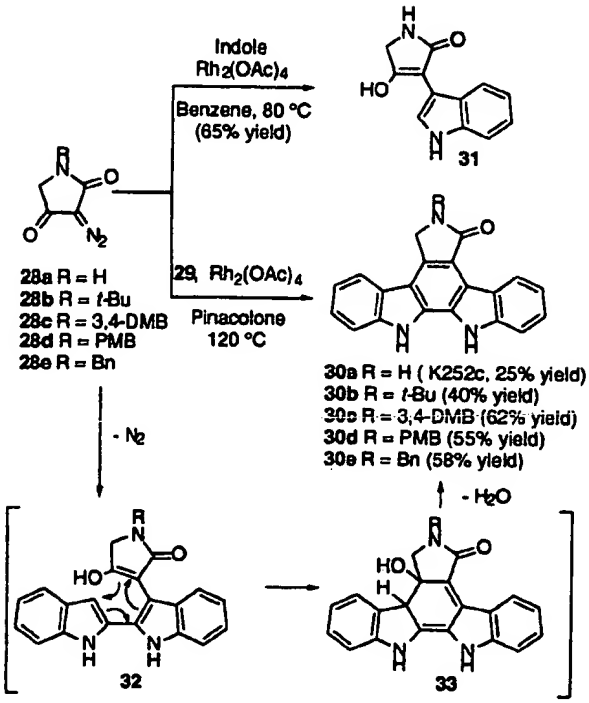


(-)-**27a** α-5-OMe
(-)-**27b** β-5-OMe

The feasibility of the carbenoid approach to **30** was initially assessed by reaction of **28a** (1.0 equiv) with indole (3.0 equiv) in the presence of catalytic $Rh_2(OAc)_4$ (0.01 equiv, Scheme XII). After only 12 h, TLC analysis indicated complete consumption of **28a** and standard work-up and isolation procedures furnished **31** in 65% yield. Similar conditions proved ineffective for the coupling of **28a** with **29**, and it was only after considerable experimentation that a procedure was developed which provided satisfactory yields of **30a**. The use of degassed pinacolone proved critical as this solvent was found to be both compatible with the carbenoid chemistry and capable of solvating the diindole substrate. Under these conditions the coupling of **28a** and **29** proceeded directly to **30a** (K252c) in 25% yield. Presumed intermediates **32** and **33** were not apparent by TLC or NMR analysis of the crude reaction mixture. In an attempt to complete the synthesis, the cycloglycosidation of **27** with **30a** revealed a tendency of the latter to alkylate at the amide nitrogen; thus, selectively protected aglycones **30b-e** were employed. Preparation of the corresponding diazolactams **28b-e**, followed by reaction with **29** in the presence of $Rh_2(OAc)_4$ (0.1 equiv) established that several protecting groups can withstand the carbenoid conditions and that the best yields (50-62%) are obtained within the benzyl class (*e.g.*, **28c,d,e→30c,d,e** Scheme XII). To

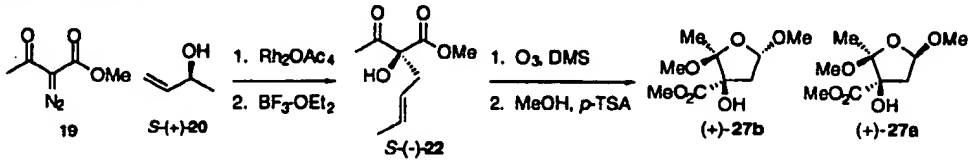
provid th most flexibility in the eventual deprotection 3,4-dimethoxybenzyl protected aglycone **28** was employed.

Sch m XII



Having gained efficient access to **30c**, attention was turned to the preparation of the furanose components (**27**). To this end, a novel tandem rearrangement protocol was developed that combines methyl 2-diazo-3-oxobutyrate (**19**) and *S*-(+)-1-buten-3-ol (**20**) to furnish (-)-**22** in a single-pot (92% ee, 75% yield). Reductive ozonolysis of (-)-**22** followed by acid promoted cyclization in methanol produced (+)-**27a** and (+)-**27b** in good yield.

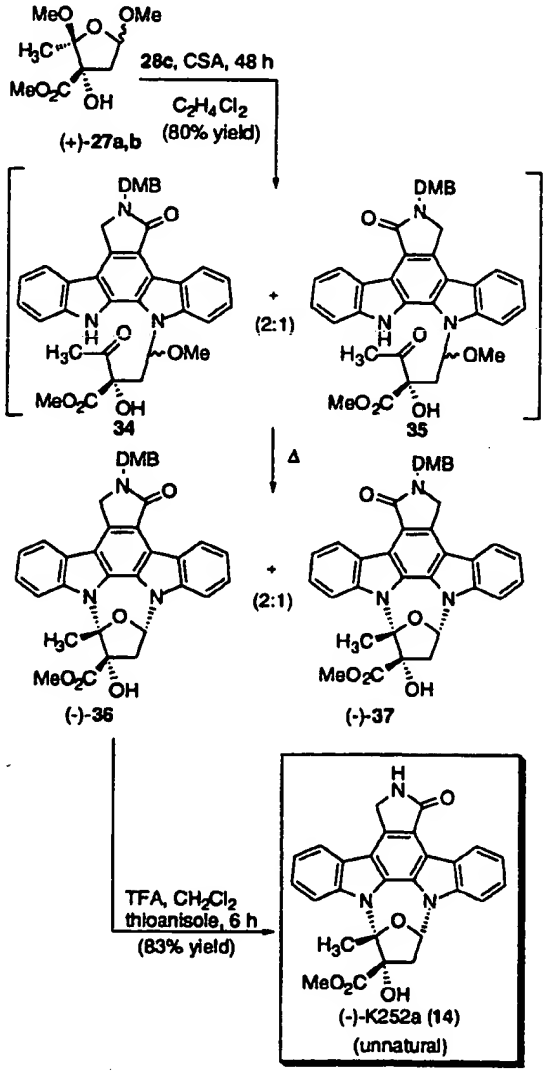
Scheme XIII



With both (+)-**27** and **30c** in hand the cycloglycosidative coupling was investigated. Of several conditions reported by McCombie, *et al.*, for related transformations, camphorsulfonic acid in 1,2-dichloroethane was found to be th catalyst and solvent of choice. In th vent, **30c** and (+)-**27a** and

27b combined rapidly to form two regioisomeric pairs of open chain monoamino acetal diastereomers (**34** and **35**). Prolonged heating of the quaternary mixture induced cycloglycosidation to only two of the four possible diastereomers.

Scheme XIV

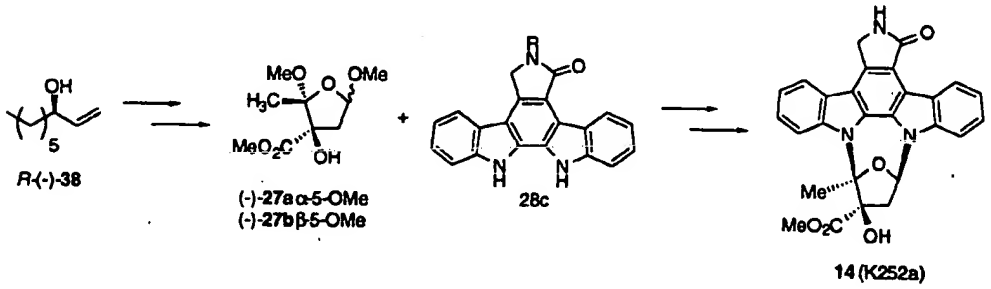


Preliminary assignment of structure was based on ^1H NMR analysis which indicated that the reaction had produced the regioisomeric products (-)-**36** (55% yield) and (-)-**37** (25% yield). The observed formation of (-)-**14** upon deprotection of (-)-**36** under standard conditions (TFA/CH_2Cl_2/thioanisole) established the cycloglycosidation as both regio- and stereoselective for th natural configuration. Comparison of synthetic

(-)-**14** to material derived from natural sources established its identity as the unnatural enantiomer of K252a.

Total synthesis of the natural enantiomer (*i.e.*, (+)-**14**) was effected in an analogous fashion using **28c** and (-)-**27a** and (-)-**27b** as coupling partners (Scheme XV). The latter compound was prepared via the tandem [3,3]/[1,2] rearrangement protocol (described in Example 1 above) using *R*-(-)-1-nonen-3-ol (**38**) as the source of asymmetry.

Scheme XV



In summary, application of a novel carbenoid mediated synthesis of K252c coupled with a highly selective tandem (3,3)/(1,2) rearrangement protocol provides efficient access to both (+)- and (-)-K252a.

Example 3

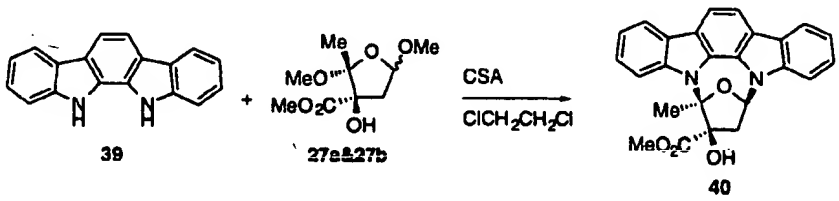
Furanosylation of Alternative Indolocarbazoles and the Interconversion of Furanosylated and Pyranosylated Indolocarbazoles

This example reports results wherein an indolocarbazole simpler than that described Example 2 is subjected to furanosylation. The derived product **40** is further manipulated into a ring-expansion substrate **41** or **42** that undergoes conversion to the corresponding pyranosylated indolocarbazole **43** or **44**, respectively (Stoltz *et al.* 1995). It is further demonstrated in this example that the α-hydroxy ketone congener **43** undergoes facile oxidative ring contraction to the furanosylated indolocarbazole upon exposure to CuCl in methanol (Stoltz *et al.* 1996).

For the furanosylation, indolo [2,3-a]carbazole (**39**) was coupled with **27a** and **27b** in a manner similar to that employed in the synthesis of

K252a desribed in Example 2. This coupling again proved highly stereoselective and produced **40** as the only isolable product in 85% yield.

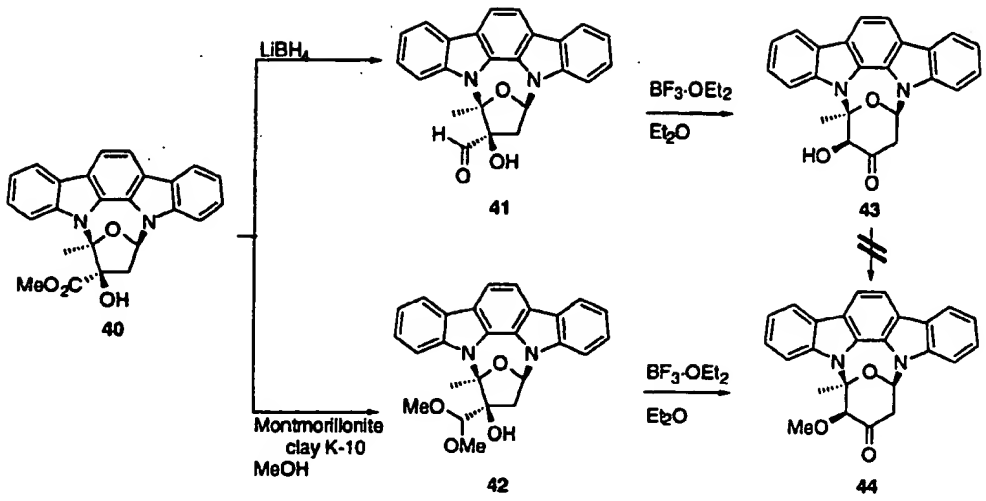
Scheme XVI



39 27a&27b 40

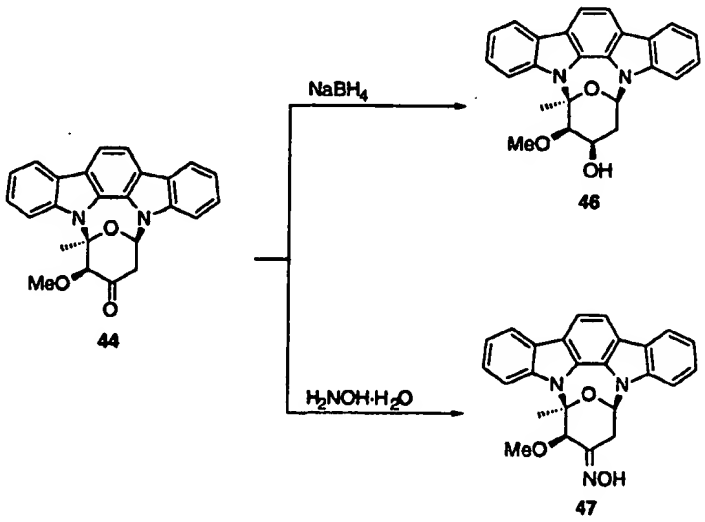
Turning to the ring expansion, it was soon discovered that transformation of **40** into aldehyde **41** followed by treatment with $BF_3 \cdot Et_2O$ results in a regio- and stereoselective rearrangement to the pyranosylated indolocarbazole **43**. At this stage all that remained for the preparation of **44** was what appeared to be a trivial alkylation of the C(3') hydroxyl. Ketone **43** surprisingly proved quite resistant to methylation under numerous alkylation conditions. In addition, attempts to incorporate directly the methyl substituent by promoting the rearrangement with a source of Me+ (*e.g.*, Meerweinís reagent, TMSOTf/TMSOMe, and MeOTf) also failed. Eventually, these difficulties led to the development of an alternative strategy that targeted dimethyl acetal **42** as the substrate for a ring expansion (Scheme XVII). Although **42** was readily produced under a variety of conditions, its instability to chromatographic purification required the employment of montmorillonite clay K-10 to promote acetal formation. Removal of the clay via filtration, solvent exchange with Et_2O, and subsequent treatment with $BF_3 \cdot Et_2O$ resulted in the slow (72 h, 25 °C) conversion of **42** to **44** (50% yield).

Scheme XVII



Having rapidly assembled α-methoxy ketone **44**, its conversion to the desamido pyranosylated indolocarbazoles was investigated. To this end, the analogs of RK-286c (**46**) and TAN-1030a (**47**) were readily prepared from **44** under standard conditions using $NaBH_4$ and $H_2NOH \cdot HCl$, respectively (Scheme XVIII).

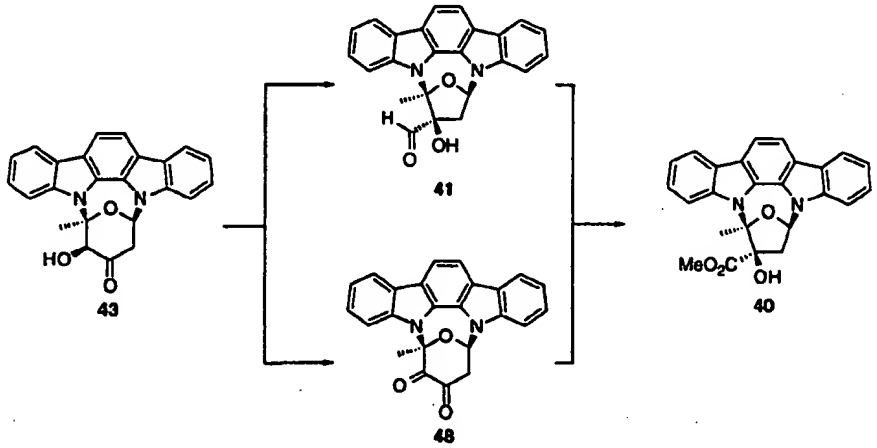
Scheme XVIII



While the above model investigations established the feasibility of a regio and stereoselective ring expansion, subsequent attempts to alkylate the derived α-hydroxy ketone **43** proved problematic. Of note is the propensity of **43** to undergo loss of the indolocarbazole nucleus as evidenced

by isolation of **39** as the major product in many of the alkylation attempts. In an effort to avoid this del terious ev nt att ntion was turned to methylation procedures that appeared to proceed under essentially neutral conditions. While these efforts failed to produce any of the desired α-methoxy ketone **44**, the conditions comprising CuCl and DCC in MeOH were observed to cleanly convert **43** to **40**, the functionalized K252a sugar moiety. Apparently these conditions induced either ring contractive α-ketol rearrangement and oxidation (*i.e.*, **43**→**41**→**40**) or oxidation and ring contractive "benzilic" acid rearrangement (*i.e.*, **43**→**48**→**40**). While not wishing to be bound to any theory, since α-hydroxy aldehyde **41** failed to undergo conversion to **40** under identical conditions, the latter of these two mechanistic possibilities appears most likely. In addition, subsequent investigations have revealed CuCl in MeOH without added DCC to be the optimal conditions for converting **43** to **40** (95% yield).

Scheme XIX



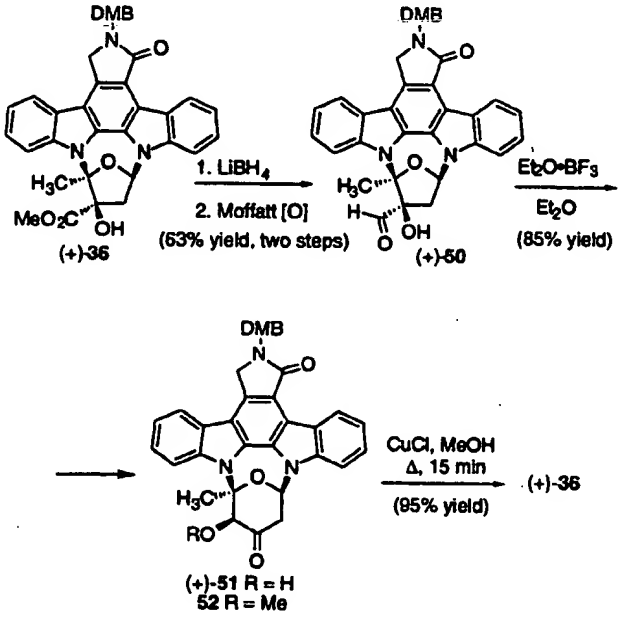
Example 4

The Synthesis of Staurosporine, RK-286c, MLR-52, and K252a

This example demonstrates that the tertiary alcohol and indolocarbazole syntheses, the indolocarbazole furanosylation, and the ring-expansion protocol described in the above Examples can be used to prepare pyranosylated indolocarbazoles that are suited for conversion to staurosporine (**49**) RK-286c (**50**), MLR-52 (**51**), and K252a (**14**) (Link *et al.*).

The synthesis of **49-51** began by converting the K252a precurs r (**36**, described above in Example 2) to the corresponding aldehyde via $LiBH_4$ reduction and then Moffatt oxidation (63% yield overall, Scheme XX). Guided by the α-ketol rearrangement results described above, **50** was exposed to $BF_3 \cdot Et_2O$ and the reaction allowed to stir at room temperature for 3 h. Given that the proposed ring-expansion of **50** to **51** could proceed to a mixture of regio- and stereoisomeric products, treatment of (+)-**50** with $BF_3 \cdot OEt_2$ in Et_2O (2.2 equiv, 25- 30 °C, 24h) surprisingly produces a single product, (+)-**51**, in 85% yield. The regio- and stereochemical outcome of this reaction, which were confirmed by spectral comparison to a closely related model and the conversion of (+)-**51** to (+)-**50** (*vide infra*).

Scheme XX

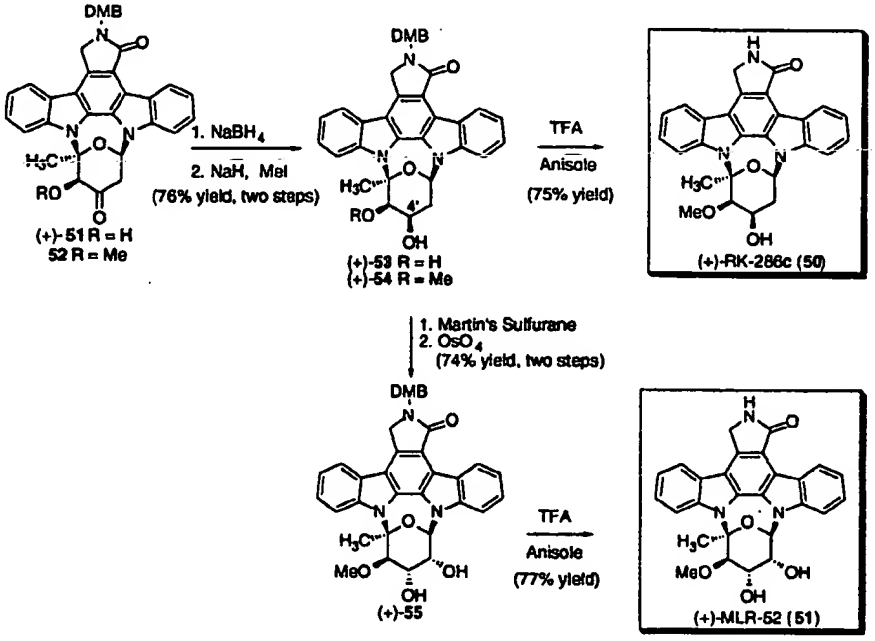


As expected from the data presented in Example 3, attempts to methylate **51** were unproductive and again led to the observation that exposure of (+)-**51** to CuCl in MeOH results in a highly stereoselective oxidation/ring-contraction sequence that produces (+)-**36** in 95% yield.

Turning from the potentially biomimetic synthesis of (+)-K252a to the synthesis of **49-51**, it was discovered that (+)-**51** undergoes selective conversion to (+)-**54** upon sequential treatment with $NaBH_4$ and NaH/MeI. Having installed all of the functional groups common to (+)-**50-51**, the

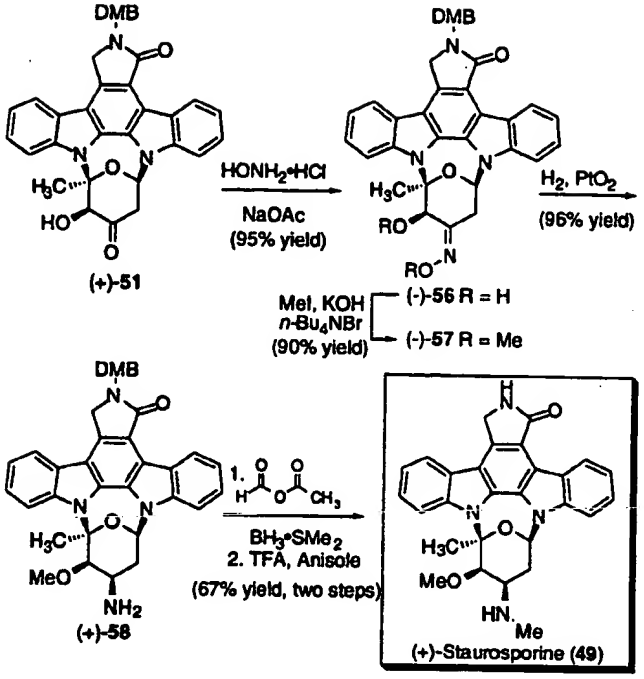
approach diverged into the synthesis of (+)-RK286c and (+)-MLR-52. The former was completed via deprotection of (+)-**54** (TFA/anisole) while the latter required a three-step sequence that was initiated by exposing (+)-**54** to Martin's sulfurane. Oxidation of the derived olefin with OsO_4 followed by deprotection of the resultant diol (+)-**55** produced (+)-**51** (Scheme XXI).

Scheme XXI



The inability to prepare α-methoxy ketone **52** guided an approach to staurosporine along a route wherein the 4' nitrogen is introduced via conversion of (+)-**51** to the corresponding oxime (-)-**56** ($H_2NOH \bullet HCl$, NaOAc, Scheme XXII). Crucial for the success of this approach is the fact that (-)-**56**, unlike ketone (+)-**51**, readily undergoes alkylation to the C(3') methyl ether (MeI, KOH, *n*-Bu_4NBr). Stereoselective reduction of the derived methoxy oxime (-)-**57** (H_2, PtO_2) to the corresponding primary amine ((+)-**58**) followed by monomethylation (HCO_2COCH_3, $BH_3 \bullet DMS$) and deprotection (TFA) produced (+)-staurosporine (**49**).

Schem XXII



In summary, efforts to devise an efficient synthesis of the pyranosylated indolocarbazoles via a common intermediate [*i.e.*, (+)-**36**] were successful in delivering (+)-**49** (19 steps), (+)-**50** (17 steps), and (+)-**51** (19 steps). In addition, these investigations have revealed both ring-expansion and -contraction reactivity that may play a central role in the biogenesis of both the furanosylated and pyranosylated members of this important class of natural products.

Example 5

Experimental Procedures for Selected Compounds in Examples 1-4

Preparation of **21**. (R)-3-Hydroxy-3-methyl-2-oxo-5-heptenoicacidethylester 2.1323 g (15.00 mmol) 2-diazomethylacetoacetate are dissolved in 75 ml benzene (1 neck 100 ml flask). Under stirring 1.0816 g (15 mmol; 1.3 ml) (S)-(+)-butenol are added to the solution. After addition of 66.3 mg (0.15 mmol; 0.01 eq.) $Rh_2(OAc)_4$ the flask is immersed into a preheated (100-110 °C) oil bath. The mixture is heated under reflux for 30 minutes. After 1 minute vigouros nitrogen evolution starts and lasts for about 2 minutes. After cooling the mixtur the solvent is evaporated and the residue is

flashed on silica (4.5 x 15 cm) using hexane/ethylacetate (20%). 1.66 g (59%) of the product are obtained. This relatively low yield (compared to the 74% obtained in the racemic series) must be due to same impurity (water?) in the butenol. b.p. 65-67°/0.35 mm Hg; IR (thin film/NaCl) 3521.0 (m), 3028.5 (w), 2981.5 (m), 2957.1 (m), 2937.9 (m), 2919.9 (m), 2857.4 (w), 1742.6 (s), 1726.1 (s), 1452.3 (m), 1437.5 (m), 1376.0 (w), 1361.2 (w), 1289.1 (m), 1250.1 (m), 1192.6 (w), 1145.8 (w), 1116.3 (w), 1081.5 (w), 1060.1 (w), 1032.1 (s), 971.9 (m), 920.3 (w), 861.6 (w), 844.7 (w), 814.4 (w), 722.7 (w), 663.1 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.57 (m, 1H), 5.35 (m, 1H), 3.88 (s, 3H), 3.28 (br.s, 1H), 2.68 (dd, J=7.0, 14.0 Hz, 1H), 2.42 (dd, J=7.7, 14.0 Hz, 1H), 1.66 (d, J=6.42 Hz, 3H), 1.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.58, 162.78, 130.97, 123.58, 78.30, 52.55, 42.26, 24.15, 17.82; HRMS (CI, isobutane) *m/z* calc'd for $C_9H_{15}O_4$ (M+H): 187.0970, found 187.0966; $[\alpha]_D^{22}$ + 14.65° (c=1.08, $CHCl_3$).

Preparation of **22**. (S)-2-Hydroxy-2-allylmethylmethylacetoacetate 3.35 g (18 mmol) (R)-3-hydroxy-3-methyl-2-oxo-5-heptenoicacidethyl-ester are dissoved in 180 ml dichloromethane and treated with 2.554 g (18 mmol; 2.21 ml) $BF_3 \cdot OEt_2$. The reaction mixture is stirred 2 hours at 25 °C (TLC control). The solvent is evaporated and the residue flashed on silica (4.5 x 18 cm) using hexane/ethylacetate (20%). 2.368 g (71%) of the product are isolated. IR (thin film/NaCl) 3476.1 (m), 3031.2 (w), 3009.6 (w), 2956.2 (m), 2921.4 (w), 2857.5 (w), 1746.9 (s), 1721.9 (s), 1437.4 (m), 1357.9 (m), 1271.0 (m), 1224.2 (m), 1195.9 (m), 1183.2 (m), 1141.0 (m), 1108.5 (m), 1076.9 (w), 1052.8 (w), 994.6 (w), 972.4 (m), 861.8 (w), 816.7 (w), 798.3 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.60 (m, 1H), 5.32 (m, 1H), 4.17 (s, 1H), 3.80 (s, 3H), 2.77 (dd, J=6.6, 14.3 Hz, 1H), 2.63 (dd, J=7.6, 14.3 Hz, 1H), 2.28 (s, 3H), 1.65 (d, J=6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.28, 170.85, 130.59, 122.91, 83.89, 53.16, 38.54, 24.76, 17.94; HRMS (CI, isobutane) *m/z* calc'd for $C_9H_{15}O_4$ (M+H): 187.0970, found 187.0969; $[\alpha]_D^{22}$ - 32.13° (c=1.08, $CHCl_3$). (S)-2-Hydroxy-2-allylmethylmethylacetoacetate (1 pot procedure) 426.5 mg (3.00 mmol) 2-diazomethylacetoacetate are dissolved in 15 ml benzene (1 neck 25 ml flask). Under stirring 237.9 mg (3.3 mmol; 0.286 ml; 1.1 eq.) (S)-(+)-butenol are added to the solution. After addition of 13.3 mg (0.03 mmol; 0.01 eq.) $Rh_2(OAc)_4$ the flask is immersed into a preheated (100-110 °C) oil bath. The mixture is heated under reflux for 30 minutes. After 1 minute vigouros

nitrogen evolution starts and lasts for about 2 minutes. After cooling the reaction mixture 554.5 mg (3.75 mmol; 0.46 ml; 1.25 eq.) $BF_3 \cdot OEt_2$ are added. The mixture is stirred for 2-3 hours (TLC control) at 25 °C. The reaction mixture is passed through silica (2.5 x 8 cm) using pentane/ether (20%) as solvent; 416.9 mg (75%) of the product are isolated.

Preparation of **27**. (S)-(+)-Hydroxy furanose and (S)-(-)-methylketonedimethylacetal 1.305 g (7.00 mmol) (S)-2-hydroxy-2-allylmethylmethylacetoacetate and a trace of sudan red dye are dissolved in 45 ml methanol. After cooling to -78 °C the mixture is treated with O_3 until the dye is completely discolored (about 3 minutes). The mixture is purged with argon for 10 Minutes at -78 °C and 20 ml dimethylsulfide are added at that temperature. The dry ice cold bath is replaced with an ice bath which is allowed to thaw (0-20 °C) over a period of 3 hours. The solvent is removed and the crude product dissoved in in 45 ml benzene. After addition of 20.0 mg (0.105 mmol; 0.015 eq.) p-toluenesulfonic acid and 12 ml methanol the mixture is stirred at 25 °C for 17 hours (until the reaction is completed as judged by TLC). The solvent is evaporated and the product is flashed on silica (4.5 x 20 cm) using hexane/ethylacetate (20%) as solvent system. 1.69 g (80%) of a mixture (1:1:1) of two furanose diastereomers and the methylketonedimethylacetal is obtained. They can be separated using HPLC. In a first run (stationary phase: SiO_2; mobile phase: hexane/dichloromethane/ethylacetate (2:2:1) a mixture of the furanose diastereomer I and the metyhylketone is eluated first followed by the second furanose diastereomer which can be isolated in its pure form. The two component mixture is separated using a different system (stationary phase: SiO_2; mobile phase: hexane/*i*-propanol (10%)). The furanose diastereomer I is eluated as first fraction closely followed by the methylketonedimethyl acetal. Hydroxyfuranose mp 81-82 °C; IR (thin film/NaCl) 3495.1 (m), 2995.3 (m), 2953.2 (s), 2917.2 (s), 2848.3 (m), 1747.11 (s), 1463.77 (m), 1439.35 (m), 1379.1 (m), 1355.2 (w), 1263.5 (s), 1200.0 (s), 1182.1 (m), 1156.1 (m), 1121.86 (s), 1086.1 (s), 1043.7 (m), 1019.3 (m), 973.677 (m), 949.3 (m), 929.7 (m), 892.27 (m), 864.6 (w), 833.7 (m), 802.7 (m), 750.6 (m), 685.5 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.07 (dd, J=0.6, 5.8 Hz, 1H), 3.79 (s, 3H), 3.42 (s, 3H), 3.38 (br. s, 1H), 3.25 (s, 3H), 3.03 (dd, J=5.8, 14.2 Hz, 1H), 2.06 (d, J=14.2 Hz, 1H), 1.54 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.50, 110.55, 103.86, 83.17, 55.56, 52.63,

49.28, 40.56, 15.82; $[\alpha]_D^{20}$ + 112.13° (c=1.06, $CHCl_3$). Methylketone IR (thin film/NaCl) 3450.0 (m), 2988.3 (m), 2953.5 (s), 2915.0 (s), 2849.2 (s), 1746 (s), 1722.3 (s), 1457.5 (m), 1436.4 (m), 1386.7 (m), 1275.0 (m), 1245.2 (m), 1198.0 (m), 1178.1 (m), 1142.1 (s), 1121.0 (s), 1063.3 (s), 1014.2 (w), 998.1 (w), 974.4 (w), 907.4 (w), 830.6 (w), 755.1 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.50 (s, 1H), 4.50 (dd, J=4.8, 6.7 Hz, 1H), 3.78 (s, 3H), 3.34 (s, 3H), 3.29 (s, 3H), 2.43 (dd, J=4.8, 14.5 Hz, 1H), 2.39 (dd, J=6.7, 14.5 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.04, 170.87, 102.01, 81.80, 54.99, 53.84, 53.22, 38.40, 24.50; $[\alpha]_D^{20}$ - 20.25° (c=0.97, $CHCl_3$). Hydroxyfuranose mp 63-64 °C; IR (thin film/NaCl) 3480.7 (m), 2995.0 (w), 2953.3 (m), 2914.2 (w), 2835.1 (w), 1726.7 (s), 1443.2 (m), 1377.9 (m), 1348.2 (w), 1278.2 (s), 1239.0 (m), 1228.0 (m), 1200.4 (m), 1181.6 (w), 1165.1 (s), 1127.6 (s), 1114.3 (s), 1092.2 (m), 1084.5 (m), 979.6 (m), 957.5 (m), 948.7 (m), 927.8 (m), 901.5 (m), 871.9 (w), 840.9 (w), 802.9 (w), 755.5 (m), 673.0 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.21 (app. t, J=5.7 Hz, 3H), 3.79 (s, 3H), 3.47 (s, 3H), 3.36 (d, J=1.6 Hz, 1H), 3.27 (s, 3H), 2.84 (ddd, J=1.6, 5.2, 14.3 Hz, 1H), 2.34 (dd, J=6.2, 14.3 Hz, 1H), 1.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.10, 1089.84, 105.38, 84.46, 56.37, 52.82, 49.00, 40.44, 14.46; HRMS (CI, isobutane) *m/z* calc'd for $C_8H_{13}O_5$ (M-CH_3OH+H): 189.0763, found 189.0764; $[\alpha]_D^{22}$ + 9.66° (c=1.03, $CHCl_3$).

Preparation of **38**. (R)-2-Hydroxy-2-allylhexylmethylacetoacetate 426.5 mg (3.00 mmol) 2-diazomethylacetoacetate are dissolved in 15 ml benzene (1 neck 25 ml flask). Under stirring 469.3 mg (3.3 mmol; 1.1 eq.) (R)-(-)-nonenol are added to the solution. After addition of 13.3 mg (0.03 mmol; 0.01 eq.) $Rh_2(OAc)_4$ the flask is immersed into a preheated (100-110 °C) oil bath. The mixture is heated under reflux for 30 minutes. After 1 minute vigouros nitrogen evolution starts and lasts for about 2 minutes. After cooling the reaction mixture 554.5 mg (3.75 mmol; 0.46 ml; 1.25 eq.) $BF_3 \cdot OEt_2$ are added. The mixture is stirred for 2-3 hours (TLC control) at 25 °C. The reaction mixture is passed through silica (2.5 x 8 cm) using pentane/ether (20%) as solvent; 510.9 mg (66%) of the product are isolated. R)-(-)-Hydroxy furanose and (R)-(+)-methylketonedimethylacetal The same procedure that was employed for the preparation of (S)-(+)-hydroxy furanose and (S)-(-)-methylketonedimethylacetal is used. 1.798 g (7.00 mmol) of (R)-2-hydroxy-2-allylhexylmethylacetoacetate are used as

starting material yielding 1.04 g (68%) of th 3 component mixture (1:1:1). Hydroxyfuranose mp 81-82 °C; IR (thin film/NaCl) 3496.4 (m), 2998.9 (m), 2953.3 (m), 2915.1 (m), 2836.9 (m), 1748.9 (s), 1732.9 (s), 1440.3 (m), 1379.3 (m), 1334.7 (w), 1261.7 (s), 1200.7 (s), 1182.7 (m), 1156.9 (s), 1122.5 (s), 1098.5 (s), 1086.5 (s), 1044.3 (m), 1021.1 (m), 975.9s, 94826 (m), 930.7 (m), 893.9 (m), 865.4 (m), 834.9 (m), 802.2 (m), 750.9 (m), 685.7 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.07 (d, J=5.8 Hz, 1H), 3.78 (s, 3H), 3.42 (s, 3H), 3.25 (s, 3H), 3.03 (dd, J=5.8, 14.1 Hz, 1H), 2.05 (d, J=14.1 Hz, 1H), 1.54 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.41, 110.46, 103.78, 83.08, 55.47, 52.52, 49.18, 40.49, 15.73; $[\alpha]_D^{20}$ - 122.55° (c=1.10, $CHCl_3$). Methylketone IR (thin film/NaCl) 3452.5 (m), 2993.2 (m), 2954.6 (m), 2934.2 (m), 2917.5 (m), 2848.4 (m), 2838.2 (m), 1748.7 (s), 1723.1 (s), 1437.8 (m), 1359.7 (m), 1275.8 (m), 1245.7 (m), 1198.5 (m), 1178.2 (m), 1144.7 (s), 1124.4 (s), 4065.4 (s), 1015.7 (m), 997.3 (m), 905.2 (m), 829.6 (w), 802.0 (w), 756.0 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.51 (br. s, 1H), 4.50 (dd, J=4.9, 6.6 Hz, 1H), 3.78 (s, 3H), 3.34 (s, 3H), 3.29 (s, 3H), 2.43 (dd, J=4.9, 14.6 Hz, 1H), 2.38 (dd, J=6.6, 14.6 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.00, 170.84, 101.96, 81.76, 54.92, 53.79, 53.18, 38.37, 24.46; $[\alpha]_D^{20}$ + 19.55° (c=1.12, $CHCl_3$). Hydroxyfuranose mp 63-64 °C; IR (thin film/NaCl) 3486.7 (m), 2994.8 (m), 2954.8 (m), 2918.0 (m), 2836.2 (m), 1732.7 (s), 1442.6 (m), 1378.3 (m), 1346.6 (w), 1276.5 (s), 1243.0 (m), 1229.7 (m), 1199.7 (m), 1183.0 (m), 1165.4 (s), 1126.7 (s), 1115.6 (s), 1086.6 (s), 1049.2 (s), 1020.2 (s), 980.1 (m), 956.6 (m), 626.1 (m), 902.6 (m), 870.2 (w), 840.2 (w), 803.0 (w), 754.6 (m), 673.3 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.21 (app. t, J=5.7 Hz, 1H), 3.79 (s, 3H), 3.47 (s, 3H), 3.36 (br. s, 1H), 3.27 (s, 3H), 2.84 (dd, J=5.3, 14.3 Hz, 1H), 2.34 (dd, J=6.2, 14.3 Hz, 1H), 1.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.11, 109.86, 105.40, 84.48, 56.39, 52.83, 49.02, 40.46, 14.48; $[\alpha]_D^{20}$ -9.00° (c=1.16, $CHCl_3$).

General method for the preparation of **30a-d** Dry N_2 is bubbled through a mixture of 2,2'-biindole (0.86 mmol), diazo compound 4 (2.2 mmol, 2.5 eq), $Rh_2(OAc)_4$ (0.086 mmol, 0.1 eq) and 8.6 mL pinacolone, in a 3-neck round bottom flask fitted with a reflux condenser for 2 h. The reaction mixture is then heated to reflux for 8 h. The mixture is allowed to cool to 25 °C, the solvent is evaporated, the residue is chromatographed (1:1 EtOAc:Hexanes) to provide (R= 3,4-DMB 0.25 g, 0.56 mmol, 65%; R=4-

PMB 0.22 g, 0.47 mmol, 55%; R=Bn 0.20 g, 0.5 mmol, 58%; R=*t*-Bu 0.13 g, 0.34 mmol, 40%).

Indolocarbazole **30a**. IR (thin film/NaCl) 3485.3 (brm), 3456.0 (brm), 3343.1 (brs), 3249.7 (brm), 2979.7 (m), 1654.4 (w), 1600.5 (s), 1578.2 (s), 1465.8 (w), 1446.5 (m), 1385.0 (s), 1364.0 (m), 1335.9 (w), 1225.3 (s) cm^{-1}; ^1H NMR (500 MHz, DMSO-d6) δ 11.45 (bs, 1H), 11.29 (bs, 1H), 9.24 (d, *J*=7.9 Hz, 1H), 8.09 (d, *J*=7.8 Hz, 1H), 7.77 (d, *J*=8.2 Hz, 1H), 7.70 (d, *J*=8.2 Hz, 1H), 7.47 (app.t, *J*=7.5 Hz, 1H), 7.41 (app.t, *J*=7.5 Hz, 1H), 7.30 (app.t, *J*=7.5 Hz, 1H), 7.21 (app.t, *J*=7.5 Hz, 1H), 5.13 (s, 2H), 1.65 (s, 9H); ^{13}C NMR (62.5 MHz, DMSO-d6) δ 169.9, 139.2, 139.0, 129.9, 127.6, 125.4, 125.3, 124.9, 122.7, 122.4, 122.0, 121.2, 119.7, 118.8, 115.1, 113.6, 111.8, 111.2, 101.9, 53.6, 48.1, 27.8; HRMS (FAB) *m/z* calc'd for $C_{24}H_{22}N_3O$ (M+H): 368.1762, found 368.1764.

Indolocarbazole **30b**. IR (thin film/NaCl) 3487.5 (brs), 3352.0 (brs), 3232.0 (brs), 3022.3 (m), 1579.1 (s), 1571.2 (s), 1517.7 (s), 1462.9 (s), 1399.3 (m), 1262.7 (m), 1237.6 (s), 1142.0 (w), 1016.8 (w), 741.3 (s) cm^{-1}; ^1H NMR (500 MHz, DMSO-d6) δ 11.50 (bs, 1H), 11.35 (bs, 1H), 9.28 (d, *J*=7.9 Hz, 1H), 7.97 (d, *J*=7.8 Hz, 1H), 7.77 (d, *J*=8.1 Hz, 1H), 7.73 (d, *J*=8.1 Hz, 1H), 7.45 (app.t, *J*=6.9 Hz, 1H), 7.44 (app.t, *J*=7.1 Hz, 1H), 7.26 (app.t, *J*=7.1 Hz, 1H), 7.25 (app.t, *J*=7.1 Hz, 1H), 7.02 (s, 1H), 6.92 (s, 2H), 4.94 (s, 2H), 4.82 (s, 2H), 3.74 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (62.5 MHz, DMSO-d6) δ 169.2, 148.9, 148.1, 139.1, 139.0, 130.6, 130.0, 127.7, 125.3, 124.9, 124.9, 124.8, 122.6, 122.3, 120.7, 119.9, 119.7, 118.8, 118.2, 115.4, 113.8, 112.3, 112.1, 111.7, 111.1, 55.5, 49.3, 45.4; HRMS (FAB) *m/z* calc'd for $C_{29}H_{24}N_3O_3$ (M+H): 462.1817, found 462.1813.

Indolocarbazole **30c**. IR (thin film/NaCl) 3429.3 (brs), 3351.3 (brs), 2912.4 (m), 1609.7 (s), 1580.3 (s), 1512.0 (s), 1465.5 (s), 1402.1 (w), 1250.61 (s), 1238.4 (s), 1177.3 (m), 1030.8 (w), 748.9 (s) cm^{-1}; ^1H NMR (500 MHz, DMSO-d6) δ 11.53 (bs, 1H), 11.37 (bs, 1H), 9.28 (d, *J*=7.8 Hz, 1H), 7.99 (d, *J*=7.7 Hz, 1H), 7.78 (d, *J*=8.1 Hz, 1H), 7.75 (d, *J*=8.1 Hz, 1H), 7.47 (app.t, *J*=7.0 Hz, 1H), 7.45 (app.t, *J*=7.1 Hz, 1H), 7.36 (d, *J*=8.4 Hz, 2H), 7.28 (app.t, *J*=7.9 Hz, 1H), 7.26 (app.t, *J*=7.8 Hz, 1H), 6.94 (d, *J*=8.5 Hz, 2H), 4.94 (s, 2H), 4.83 (s, 2H), 3.72 (s, 3H); ^{13}C NMR (62.5 MHz, DMSO-d6) δ 169.2, 158.4, 139.1, 139.0, 130.0, 129.9, 128.9, 127.7, 125.3, 124.9, 124.8,

122.6, 122.2, 120.7, 119.7, 118.8, 118.2, 115.4, 113.9, 113.8, 111.7, 111.1, 54.9, 49.2, 45.0; HRMS (FAB) *m/z* calc'd for $C_{28}H_{22}N_3O_2$ (M+H): 432.1712, found 432.1699.

(+)-N-3,4-Dimethoxybenzyl-K252a (**36**). Aglycone **30c** (0.22 mmol) and (-)-2,5-dimethoxy sugar (0.87 mmol, 4.0 eq) were refluxed in dry 1,2-dichloroethane (7.5 mL) in the presence of camphorsulfonic acid (0.022 mmol, 0.1 eq) for 48 h. The reaction mixture was allowed to cool to 25 °C, diluted with 5.0 mL CH_2Cl_2, and washed with 5.0 mL 10% $NaHCO_3$ sln. The organic layer was evaporated and purified by preparative tlc (1:60, MeOH:70% CH_2Cl_2 / hexanes, 3 elutions) giving (+)-**36** (75.0 mg, 0.120 mmol, 55%) and (+)-**37** (34.0 mg, 0.055 mmol, 25%).

Indolocarbazole (+)-**36**. IR (thin film/NaCl) 3279.7 (brm), 3012.1 (m), 2952.1 (m), 2930.1 (m), 2850.1 (w), 1732.2 (m), 1646.2 (s), 1590.4 (m), 1513.7 (s), 1460.2 (s), 1260.3 (s), 1139.5 (s), 1028.1 (m), 744.5 (s) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 9.26 (d, *J*=7.9 Hz, 1H), 7.99 (d, *J*=7.7 Hz, 1H), 7.92 (app.t, *J*=8.0 Hz, 2H), 7.49 (app.t, *J*=7.7 Hz, 1H), 7.47 (app.t, *J*=7.8 Hz, 1H), 7.32 (app.t, *J*=7.9 Hz, 1H), 7.30 (app.t, *J*=8.1 Hz, 1H), 7.15 (dd, *J*=5.2, 6.9 Hz, 1H), 7.02 (s, 1H), 6.94 (d, *J*=9.0 Hz, 1H), 6.92 (d, *J*=9.0 Hz, 1H), 6.35 (s, 1H), 5.0 (dd, *J*=17.8, 25.9 Hz, 2H), 4.84 (dd, *J*=15.5, 17.5 Hz, 2H), 3.92 (s, 3H), 3.74 (s, 3H), 3.71 (s, 3H), 3.39 (dd, *J*=7.3, 14.0 Hz, 1H), 2.13 (s, 3H), 2.00 (dd, *J*=4.7, 14.0 Hz, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 172.6, 168.6, 148.9, 148.2, 139.8, 136.7, 130.4, 130.0, 128.2, 125.3, 125.3, 124.8, 123.9, 123.8, 122.4, 120.9, 120.2, 119.8, 119.3, 118.9, 115.6, 114.6, 114.2, 112.3, 112.1, 108.8, 99.3, 84.8, 55.5, 52.4, 49.5, 45.4, 42.4, 22.6; HRMS (FAB) *m/z* calc'd for $C_{36}H_{32}N_3O_7$ (M+H): 618.2240, found 618.2240; $[\alpha]_D^{20}$ (+)-15° (*c*=0.1, MeOH).

Indolocarbazole (+)-**37**. IR (thin film/NaCl) 3462.3 (brm), 3014.0 (m), 2952.3 (m), 2925.1 (m), 2849.7 (m), 1730.8 (s), 1645.0 (m), 1514.7 (m), 1455.6 (s), 1403.9 (m), 1348.5 (m), 1312.6 (m), 1257.2 (s), 1235.0 (s), 1138.1 (s), 1068.8 (m), 1027.3 (m), 750.3 (s) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 9.54 (d, *J*=7.9 Hz, 1H), 8.01 (d, *J*=7.9 Hz, 1H), 7.94 (d, *J*=8.2 Hz, 1H), 7.89 (d, *J*=8.5 Hz, 1H), 7.50 (app.t, *J*=7.5 Hz, 1H), 7.45 (app.t, *J*=7.5 Hz, 1H), 7.30 (app.t, *J*=7.5 Hz, 1H), 7.29 (app.t, *J*=7.6 Hz, 1H), 7.14 (dd, *J*=5.0, 7.2 Hz, 1H), 7.01 (d, *J*=0.71 Hz, 1H), 6.92 (app.t, *J*=8.2 Hz, 1H), 6.92 (dd, *J*=1.1, 8.4 Hz, 1H), 6.34 (bs, 1H), 4.97 (dd, *J*=17.9, 21.3 Hz, 2H), 4.83 (dd, *J*=15.1, 21.9 Hz, 2H), 3.92 (s, 3H), 3.74 (s, 3H), 3.71 (s, 3H), 3.40

(dd, J=7.5, 14.0 Hz, 1H), 2.14 (s, 3H), 2.05 (dd, J=4.8, 14.0 Hz, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 172.6, 168.9, 149.0, 148.2, 139.7, 136.8, 130.4, 126.2, 126.1, 125.4, 125.1, 124.9, 124.3, 122.0, 121.3, 120.2, 119.8, 119.2, 118.7, 116.3, 113.9, 113.8, 112.3, 112.1, 109.4, 99.3, 84.9, 84.8, 55.5, 52.4, 49.0, 45.4, 42.5, 22.8; HRMS (FAB) m/z calc'd for $C_{36}H_{32}N_3O_7$ (M+H): 618.2240, found 618.2240; $[\alpha]_D^{20}$ (+)-13° (c=0.1, MeOH).

(+)-K252a (**14**). To a stirred solution of (+)-**36** (17.0 mg, 0.028 mmol) in CH_2Cl_2 (1.4 mL) at 25 °C was added thioanisole (0.16 mL, 1.4 mmol, 50 eq) followed by 2,2,2-trifluoroacetic acid (1.4 mL). The solution was stirred for 6 h, at which point 2.0 mL sat. $NaHCO_3$ sln. was added dropwise to neutralize the reaction mixture, the organic layer was separated, evaporated and purified via preparative tlc (1:40, MeOH:50% CH_2Cl_2/ hexanes, 3 elutions) giving (+)-K252a (10.8 mg, 0.023 mmol, 83%).

Preparation of desamido K252a (**40**) To a suspension of indolo[2.3-a]carbazole (10) (1.0 g, 3.9 mmol) in 1,2-dichloroethane (130 mL) was added furanose 9 (1.8 g, 8.2 mmol) followed by CSA (100 mg, 0.43 mmol). The suspension was heated at reflux for 48 h, following which the reaction was allowed to cool to room temperature and was diluted with CH_2Cl_2 (100mL), washed with 10% $NaHCO_3$ (aq.), dried over Na_2SO_4 and chromatographed on silica gel using 3:1 hexanes:ethyl acetate as eluent to afford indolocarbazole **40** (1.37 g, 85%) as a yellow foam. ^1H NMR (500 MHz, acetone-d_6): δ 8.18 (app.t, J=6.6 Hz, 1H), 8.18 (app.t, J=5.4 Hz, 1H), 8.00 (m, 2H), 7.89 (d, J=8.5 Hz, 1H), 7.75 (d, J=8.2 Hz, 1H), 7.44 (td, J=0.9, 7.6 Hz, 1H), 7.38 (td, J=1.0, 7.9 Hz, 1H), 7.26 (app.t, J=6.9 Hz, 1H), 7.25 (app.t, J=7.1 Hz, 1H), 7.10 (dd, J=4.9, 7.3 Hz, 1H), 5.18 (s, 1H), 3.99 (s, 3H), 3.44 (dd, J=7.5, 14.0 Hz, 1H), 2.21 (s, 3H), 2.19 (dd, J=4.9, 14.0 Hz, 1H). ^{13}C NMR (125 MHz, acetone-d_6): δ 174.1, 140.8, 138.1, 127.7, 127.0, 125.6, 125.6, 125.5, 125.4, 121.6, 121.5, 121.2, 120.5, 120.4, 120.3, 115.0, 113.1, 112.8, 109.6, 99.9, 86.1, 86.0, 53.3, 43.2, 23.3. IR (thin film/NaCl): 3501.3 (brm), 3047.5 (m), 3006.7 (m), 2950.6 (m), 1729.4 (s), 1640.2 (m), 1568.1 (m), 1441.1 (s), 1305.9 (s), 1230.3 (s), 1128.1 (s), 740.0 (s) cm^{-1}. HRMS (EI) m/z Calc'd for $C_{25}H_{20}N_2O_4$: 412.1423. Found: 412.1419.

Preparation of aldehyde **41** To a stirred solution of ester 11 (1.0 g, 2.43 mmol) in THF (24.3mL), was added $LiBH_4$ (106 mg, 4.85 mmol) at room

temperature. After 20 min the solvent was removed in vacuo. To the white residue was added 50 mL 1.0 N HCl on an ice bath. The aqueous phase was extracted with CH_2Cl_2 (3x 50mL). The combined organic phases were dried with Na_2SO_4 and chromatographed on silica gel using 1:1 hexanes:ethyl acetate as eluent to afford a diol (815 mg, 87%) as a white solid. ^1H NMR (500 MHz, acetone-d6): δ 8.18 (d, J=7.6 Hz, 1H), 8.15 (d, J=7.8 Hz, 1H), 7.96 (s, 2H), 7.89 (d, J=8.5 Hz, 1H), 7.65 (d, J=8.1 Hz, 1H), 7.42 (app.t, J=7.6 Hz, 1H), 7.36 (app.t, J=8.2 Hz, 1H), 7.25 (app.t, J=7.6 Hz, 1H), 7.23 (app.t, J=7.4 Hz, 1H), 6.91 (dd, J=5.2, 7.4 Hz, 1H), 4.57 (s, 1H), 4.18 (app.t, J=5.9 Hz, 1H), 4.06 (dd, J=5.4, 11.1 Hz, 1H), 3.90 (dd, J=7.1, 11.1 Hz, 1H), 3.30 (dd, J=7.6, 13.8 Hz, 1H), 2.23 (dd, J=5.1, 13.8 Hz, 1H), 2.22 (s, 3H). ^{13}C NMR (125 MHz, acetone-d6): δ 140.2, 137.4, 127.6, 126.3, 125.4, 125.0, 124.6, 124.6, 120.7, 120.6, 119.9, 119.5, 114.6, 112.2, 112.0, 108.8, 100.1, 84.2, 83.8, 65.5, 40.6, 21.5. IR (thin film/NaCl): 3416.8 (brs), 3052.9 (m), 3010.5 (m), 2955.4 (w), 1732.7 (w), 1640.9 (m), 1568.5 (m), 1492.6 (m), 1459.0 (s), 1441.4 (s), 1309.0 (s), 1233.1 (s), 1031.9 (s), 741.0 (s) cm^{-1}. HRMS (EI) *m/z* Calc'd for $C_{24}H_{20}N_2O_3$: 384.1474. Found: 384.1472. To a stirred solution of the diol (500 mg, 1.3 mmol) in 1:1 benzene:DMSO (8.7 mL) was added pyridinium trifluoroacetate (250 mg, 1.3 mmol) followed by 1,3-dicyclohexylcarbodiimide (810 mg, 3.9 mmol). The flask was then quickly sealed with a septum, evacuated, and flushed with N_2 (3x). The heterogeneous mixture was stirred for 7h until reaction was complete as indicated by TLC. Benzene (15 mL) was added to the mixture and the 1,3-dicyclohexylurea (DCU) precipitate was filtered. The filtrate was washed with H_2O (3x20 mL), and the combined aqueous layers were back extracted with CH_2Cl_2 (3x30mL). All organic layers were combined, dried with Na_2SO_4, and evaporated to an oily residue. A minimum amount of acetone (2 mL) was added to precipitate the remaining DCU. Filtration and evaporation to a yellow oil, which was puified by MPLC (3:1 hexanes:ethyl acetate) gave aldehyde **41** (375 mg, 73%, 63% 2 steps) as a yellow powder. ^1H NMR (500 MHz, $CDCl_3$): δ 9.70 (s, 1H), 7.99 (app.t, J=7.3 Hz, 2H), 7.78 (s, 2H), 8.02 (d, J=8.4 Hz, 1H), 7.29 (app.t, J=7.4 Hz, 1H), 7.24 (app.t, J=7.2 Hz, 1H), 7.22 (d, J=8.4 Hz, 1H), 7.17 (app.t, J=7.9 Hz, 1H), 7.15 (app.t, J=7.2 Hz, 1H), 6.59 (dd, J=5.0, 7.4 Hz, 1H), 3.08 (s, 1H), 2.76 (dd, J=7.6, 14.6 Hz, 1H), 1.99 (s, 3H), 1.83 (dd, J=5.0, 14.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.4, 139.3, 136.9, 126.3, 126.3, 125.1, 124.7, 124.1, 121.2, 121.1, 120.8, 120.3, 120.3, 119.9, 113.1,

112.9, 112.2, 108.0, 97.7, 87.7, 84.0, 39.7, 23.0. IR (thin film/NaCl): 3486.7 (brm), 3054.6 (m), 3007.7 (m), 2945.3 (m), 2843.4 (w), 1723.9 (m), 1641.8 (m), 1568.6 (m), 1458.7 (m), 1441.1 (s), 1309.2 (s), 1232.5 (s), 1128.8 (m), 1004.2 (m), 741.7 (s) cm^{-1}.HRMS (EI) *m/z* Calc'd for $C_{24}H_{18}N_2O_3$: 382.1317. Found: 382.1319.

Preparation of hydroxy ketone **43** To a suspension of aldehyde 12 (75 mg, 0.196 mmol) in Et_2O (5.0 mL) was added $BF_3 \cdot OEt_2$ (27 μL, 0.216 mmol) and the mixture stirred vigorously for 6h. CH_2Cl_2 (25 mL) was added to solubilize the suspension and the resulting solution was evaporated onto SiO_2 (100mg) and chromatographed using 2:1 hexanes:ethyl acetate as eluent to provide ketone **43** (47 mg, 60%) as a white powder. ^1H NMR (500 MHz, $CDCl_3$): δ 8.15 (d, J=7.7 Hz, 1H), 8.10 (d, J=7.7 Hz, 1H), 7.97 (d, J=8.5 Hz, 1H), 7.92 (d, J=8.2 Hz, 1H), 7.90 (d, J=8.2 Hz, 1H), 7.43 (app.t, J=7.7 Hz, 1H), 7.39 (app.t, J=7.8 Hz, 1H), 7.32 (app.t, J=7.4 Hz, 1H), 7.28 (app.t, J=7.5 Hz, 1H), 7.25 (d, J=8.1 Hz, 1H), 7.06 (d, J=7.3 Hz, 1H), 4.89 (d, J=6.0 Hz, 1H), 3.55 (dd, J=7.5, 14.3 Hz, 1H), 3.49 (d, J=6.5 Hz, 1H), 2.99 (d, J=14.4 Hz, 1H), 2.54 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.8, 140.2, 136.3, 126.4, 125.7, 125.4, 125.1, 124.8, 124.6, 121.4, 120.8, 120.4, 120.2, 119.8, 115.2, 112.7, 112.4, 112.1, 107.9, 100.3, 84.03, 81.6, 44.7, 29.5. IR (thin film/NaCl): 3328.6 (brm), 3048.0 (w), 2923.7 (m), 2852.1 (w), 1731.4 (s), 1637.4 (m), 1441.5 (s), 1395.3 (m), 1312.0 (s), 1130.1 (m), 740.8 (s) cm^{-1}. HRMS (EI) *m/z* Calc'd for $C_{24}H_{18}N_2O_3$: 382.1317. Found: 382.1315.

Preparation of methoxy ketone **44** Montmorillonite Clay K-10 (1.2 g) was premixed with trimethylorthoformate (1.78 mL, 16.3 mmol) and immediately transfer to a stirred solution of aldehyde 12 (414 mg, 1.1 mmol) in $CHCl_3$ (11 mL) aided by an additional 3 mL $CHCl_3$. The reaction was monitored by TLC (3:1 hexanes:ethyl acetate) and after approximately 0.5 h formation of the dimethyl acetal 16 was complete. The reaction mixture was filtered, and the filtrate evaporated *in vacuo*. The residue was dissolved in diethyl ether (110 mL) under an inert atmosphere, followed by addition of $BF_3 \cdot OEt_2$ (2.85 mL, 23.1 mmol). The mixture was stirred for 4 d at 25 °C, following which triethyl amine (6.1 mL) and CH_2Cl_2 (100 mL) were added, the solution was evaporated under reduced pressure and chromatographed on silica gel using 2:1 hexanes:ethyl acetate as eluent to afford methoxy ketone **44** (214 mg, 50%) as a yellow foam. ^1H NMR (500

MHz, DMSO-d6): δ 8.21 (d, J=7.7 Hz, 1H), 8.16 (d, J=7.8 Hz, 1H), 7.97 (d, J=8.2 Hz, 1H), 7.95 (d, J=8.2 Hz, 1H), 7.88 (d, J=8.6 Hz, 1H), 7.68 (d, J=8.1 Hz, 1H), 7.46 (td, J=1.0, 7.4 Hz, 1H), 7.37 (td, J=1.1, 7.7 Hz, 1H), 7.36 (d, J=7.2 Hz, 1H), 7.30 (app.t, J=7.6 Hz, 1H), 7.23 (app.t, J=7.4 Hz, 1H), 5.02 (s, 1H), 3.94 (dd, J=7.2, 13.7 Hz, 1H), 3.39 (s, 3H), 2.62 (d, J=13.9 Hz, 1H), 2.52 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d6): δ 199.8, 139.4, 135.7, 125.0, 124.8, 124.5, 124.1, 124.0, 120.0, 119.8, 119.4, 119.2, 114.9, 112.1, 111.3, 109.2, 99.0, 88.2, 84.4, 58.9, 45.4, 29.2. IR (thin film/NaCl): 3046.6 (brm), 3003.8 (brw), 2927.9 (m), 2835.6 (m), 1736.6 (s), 1640.5 (m), 1565.8 (m), 1492.7 (m), 1442.9 (s), 1311.5 (s), 1144.3 (m), 1126.1 (s), 740.2 (s) cm^{-1}. HRMS (EI) *m/z* Calc'd for $C_{25}H_{20}N_2O_3$: 396.1474. Found: 396.1474.

Preparation of desamido TAN-1030a (**47**) A suspension of ketone 15 (30 mg, 0.08 mmol), hydroxylamine hydrochloride (17 mg, 0.24 mmol), and NaOAc (20 mg, 0.24 mmol) in 50% aqueous EtOH (2.0 mL) was heated gently to reflux for 30 min. Following cooling to room temperature, sovent was removed *in vacuo*, and the residue purified by MPLC (2:1 hexanes:ethyl acetate) to provide oxime **47** (26 mg, 85%) as a yellow powder. ^1H NMR (500 MHz, DMSO-d6): δ 10.43 (s, 1H), 8.17 (d, J=7.8 Hz, 1H), 8.13 (d, J=7.4 Hz, 1H), 7.91 (d, J=8.4 Hz, 1H), 7.89 (d, J=8.4 Hz, 1H), 7.88 (d, J=8.4 Hz, 1H), 7.67 (d, J=8.2 Hz, 1H), 7.44 (app.t, J=7.6 Hz, 1H), 7.34 (app.t, J=7.7 Hz, 1H), 7.27 (app.t, J=7.5 Hz, 1H), 7.20 (app.t, J=7.4 Hz, 1H), 6.98 (d, J=5.5 Hz, 1H), 4.70 (s, 1H), 3.61 (d, J=14.1 Hz, 1H), 3.42 (s, 3H), 2.97 (dd, J=5.7, 14.3 Hz, 1H), 2.42 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d6): δ 145.3, 139.3, 135.9, 126.0, 125.1, 124.9, 124.6, 124.2, 124.0, 120.0, 119.6, 119.4, 119.1, 119.1, 115.0, 111.8, 111.0, 109.1, 95.9, 83.7, 82.2, 58.3, 29.7, 28.4. IR (thin film/NaCl): 3249.5 (brm), 2918.3 (s), 2848.4 (s), 1728.1 (m), 1640.2 (m), 1443.1 (s), 1398.1 (m), 1312.0 (m), 1124.5 (s), 740.7 (s) cm^{-1}. HRMS (EI) *m/z* Calc'd for $C_{25}H_{21}N_3O_3$: 411.1583. Found: 411.1582.

Preparation of desamido RK-286c (**46**) To a stirred solution of ketone 15 (12 mg, 0.03 mmol) in 1:1 MeOH: CH_2Cl_2 (1.0 mL) was added $NaBH_4$ (3 mg, 0.08 mmol) at room temperature. After 5 minutes solvent was removed under reduced pressure. To the white residue was added 1 mL 1.0 N HCl on an ice bath. The mixture was stirred for 15 min at 25 °C and extracted with CH_2Cl_2 (3x 1mL). The combined organic phases were dried with Na_2SO_4 and chromatographed on silica gel using 2:1 hexanes:ethyl

acetate as eluent to afford alcohol **46** (12 mg, 95%) as a white solid. ^1H NMR (500 MHz, $CDCl_3$): δ 8.14 (d, J=7.7 Hz, 1H), 8.11 (d, J=7.7 Hz, 1H), 7.90 (d, J=8.2 Hz, 1H), 7.85 (d, J=8.2 Hz, 1H), 7.81 (d, J=8.5 Hz, 1H), 7.39 (td, J=1.0, 8.1 Hz, 1H), 7.35 (ddd, J=.14, 7.1, 8.4 Hz, 1H), 7.25 (m, 3H), 6.54 (d, J=5.6 Hz, 1H), 4.34 (m, 1H), 3.66 (d, J=3.0 Hz, 1H), 3.53 (s, 3H), 2.71.dd (3.5, J=14.9 Hz, 1H), 2.45 (m, 1H), 2.30 (s, 3H), 1.66 (bs, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.6, 136.6, 128.3, 127.2, 126.5, 126.2, 124.8, 124.4, 123.9, 120.5, 120.3, 119.6, 119.3, 114.9, 112.1, 110.9, 107.6, 90.6, 83.1, 79.7, 60.5, 57.4, 33.7, 29.9. IR (thin film/NaCl): 3528.3 (brm), 3048.1 (m), 3000.2 (m), 2928.4 (m), 1643.7 (m), 1564.8 (m), 1493.3 (m), 1445.1 (s), 1344.4 (m), 1311.6 (s), 1231.2 (s), 1109.5 (brs) cm^{-1}. HRMS (EI) *m/z* Calc'd for $C_{25}H_{22}N_2O_3$: 398.1630. Found: 398.1633.

Preparation of aldehyde (+)-**50** To a stirred solution of ester (+)-**36** (150 mg, 0.243mmol) in THF (2.5 mL) was added $LiBH_4$ (12 mg, 0.535 mmol) at room temperature. After 20 min solvent was removed in vacuo. To the white residue, 10.0 mL 1.0 N HCl was added on an ice bath. The aqueous phase was extracted with CH_2Cl_2 (3x 20 mL). The combined organic phases were dried with Na_2SO_4 and chromatographed on silica gel using 1:1 hexanes:ethyl acetate as eluent to afford a diol (124mg, 89%) as a white solid. ^1H NMR (500 MHz, DMSO-d_6): δ 9.25 (d, J=7.9 Hz, 1H), 7.97 (d, J=7.2 Hz, 1H), 7.96 (d, J=8.1 Hz, 1H), 7.78 (d, J=8.3 Hz, 1H), 7.48 (app.t, J=7.6 Hz, 1H), 7.43 (app.t, J=7.8 Hz, 1H), 7.29 (app.t, J=7.1 Hz, 1H), 7.28 (app.t, J=7.2 Hz, 1H), 7.02 (s, 1H), 7.96 (dd, J=5.2, 7.2 Hz, 1H), 6.94 (s, 2H), 5.33 (s, 1H), 5.06 (t, J=5.6 Hz, 1H), 5.02 (d, J=17.7 Hz, 1H), 4.95 (d, J=17.6 Hz, 1H), 4.85 (d, J=15.9 Hz, 1H), 4.85 (d, J=15.7 Hz, 1H), 3.85-3.81 (m, 2H), 3.75 (s, 3H), 3.72 (s, 3H), 3.14 (dd, J=7.6, 13.7 Hz, 1H), 2.15 (s, 3H), 1.94 (dd, J=4.8, 13.7 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 168.9, 148.9, 148.1, 140.0, 136.7, 130.5, 130.2, 128.7, 125.4, 125.3, 124.6, 124.3, 123.8, 122.4, 120.9, 120.0, 119.8, 119.2, 118.5, 115.2, 114.9, 114.0, 112.1, 111.8, 108.7, 100.2, 83.5, 64.7, 55.5, 55.5, 49.6, 45.4, 40.2, 40.1, 21.3. IR (thin film/NaCl): 3343.8 (brm), 3001.5 (w), 2950.7 (m), 2926.1 (m), 1647.4 (s), 1588.0 (m), 1514.4 (m), 1459.7 (s), 1422.2 (m), 1399.6 (m), 1312.4 (m), 1138.0 (s), 744.7 (s) cm^{-1}. $[\alpha]_D^{25}$ +112° (c=0.1, MeOH). To a stirred solution of the diol (395 mg, 0.67 mmol) in 1:1 benzene:DMSO (4.6 mL) was added pyridinium trifluoroacetate (130 mg, 0.67 mmol) followed by 1,3-dicyclohexylcarbodiimide (415 mg, 2.01 mmol). The flask was then quickly

sealed with a septum, evacuated, and flushed with N_2 (3x). The heterogeneous mixture was stirred for 9h until reaction was complete as indicated by TLC. Benzene (5.0 mL) was added to the mixture and the 1,3-dicyclohexylurea (DCU) precipitate was filtered. The filtrate was washed with H_2O (3x 5.0 mL), and the combined aqueous layers were back extracted with CH_2Cl_2 (3x 10.0 mL). All organic layers were combined, dried with Na_2SO_4, and evaporated to an oily residue. A minimum amount of acetone (2 mL) was added to precipitate the remaining DCU. Filtration and evaporation to a yellow oil, which was puified by MPLC (2:1→1:1 hexanes:ethyl acetate) gave aldehyde (+)-**50** (280 mg, 71%, 63% 2 steps) as a yellow powder. ^1H NMR (500 MHz, DMSO-d_6): δ 10.07 (s, 1H), 9.31 (d, J=7.9 Hz, 1H), 8.02 (d, J=8.5 Hz, 1H), 7.99 (d, J=7.7 Hz, 1H), 7.87 (d, J=8.2 Hz, 1H), 7.50 (app.t, J=8.1 Hz, 1H), 7.47 (app.t, J=8.2 Hz, 1H), 7.32 (app.t, J=8.1 Hz, 1H), 7.17 (dd, J=7.2, 4.8 Hz, 1H), 7.04 (s, 1H), 6.94 (d, J=9.6 Hz, 1H), 6.93 (d, J=8.1 Hz, 1H), 6.57 (bs, 1H), 5.02 (d, J=17.6 Hz, 1H), 4.98 (d, J=17.7 Hz, 1H), 4.87 (d, J=15.2 Hz, 1H), 4.83 (d, J=15.2 Hz, 1H), 3.76 (s, 3H), 3.73 (s, 3H), 3.24 (dd, J=7.6, 14.0 Hz, 1H), 2.22 (s, 3H), 2.00 (dd, J=4.5, 14.0 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 202.2, 168.7, 148.9, 148.1, 139.9, 136.9, 130.4, 130.2, 128.2, 125.5, 125.1, 123.9, 123.9, 122.5, 121.1, 120.4, 119.9, 119.6, 119.1, 115.8, 114.6, 114.4, 112.1, 111.8, 109.0, 98.7, 86.8, 84.3, 55.5, 55.5, 49.6, 45.5, 39.4, 22.7. IR (thin film/NaCl): 3253.9 (brm), 3010.7 (m), 2953.6 (m), 2934.0 (m), 2833.9 (s), 1734.0 (s), 1646.2 (s), 1614.7 (w), 1589.9 (m), 1514.1 (m), 1399.1 (s), 1275.7 (m), 1138.4 (s), 1024.8 (m), 745.1 (s) cm^{-1}. $[\alpha]_D^{25}$ +48° (c=0.1, MeOH).

Preparation of hydroxy ketone (+)-**51** To a suspension of aldehyde (+)-**50** (100 mg, 0.170 mmol) in Et_2O (17.0 mL) was added $BF_3 \cdot OEt_2$ (23 μL, 0.187 mmol) and the mixture stirred vigorously for 12h at 25-30 °C, when again was treated with $BF_3 \cdot OEt_2$ (23 μL, 0.187 mmol) and stirred for an additional 12 h at the same temperature. The reaction mixture was filtered to provide ketone (+)-**51** (85 mg, 85%) as a white powder. ^1H NMR (500 MHz, DMSO-d_6, 310 K): δ 9.35 (d, J=7.9 Hz, 1H), 8.06 (d, J=8.6 Hz, 1H), 7.92 (d, J=7.7 Hz, 1H), 7.72 (d, J=8.2 Hz, 1H), 7.53 (app.t, J=7.6 Hz, 1H), 7.43 (app.t, J=8.1 Hz, 1H), 7.40 (d, J=6.6 Hz, 1H), 7.35 (app.t, J=7.5 Hz, 1H), 7.29 (app.t, J=7.4 Hz, 1H), 7.02 (s, 1H), 6.93 (s, 2H), 6.12 (d, J=5.1 Hz, 1H), 5.23 (d, J=4.5 Hz, 1H), 4.96 (s, 2H), 4.85 (d, J=15.1 Hz, 1H), 4.81 (d, J=15.1 Hz, 1H), 3.97 (dd, J=6.7, 14.1 Hz, 1H), 3.75 (s, 3H), 3.72 (s, 3H),

2.66 (d, J=14.1 Hz, 1H), 2.54 (s, 3H). ^{13}C NMR (500 MHz, DMSO-d6): δ 201.1, 168.6, 148.9, 148.1, 140.3, 136.0, 130.4, 129.8, 126.9, 125.6, 125.5, 124.9, 124.0, 123.6, 122.8, 120.7, 120.4, 119.9, 119.9, 118.8, 115.9, 115.1, 114.3, 112.1, 111.8, 109.2, 100.5, 84.4, 80.0, 55.5, 55.5, 49.6, 45.4, 44.9, 29.4. IR (thin film/NaCl): 3300.0 (brs), 2999.5 (brm), 2848.6 (m), 1728.9 (m), 1665.5 (s), 1503.3 (m), 1451.2 (s), 1406.8 (m), 1132.8 (s), 1021.9 (m), 750.6 (s) cm^{-1}. $[\alpha]_D^{25}$ +83° (c=0.1, DMSO).

Preparation of Ester (+)-**35** To a solution of ketone (+)-**51** (10 mg, 0.017 mmol) in 1:1 MeOH/CH_2Cl_2 (1.0 mL) was added Copper (I) chloride (30 mg, 0.30 mmol), and the mixture warmed to reflux for 15 min. Solvent was removed *in vacuo* and the resulting residue subjected to silica gel chromatography (1:1, hexanes:ethyl acetate) to afford (+)-**36** (10 mg, 95%) as a colorless solid.

Preparation of diol (+)-**53** To a stirred solution of ketone (+)-**51** (85 mg, 0.15 mmol) in 1:1:2 MeOH:CH_2Cl_2:$CHCl_3$ (20.0 mL), $NaBH_4$ (20 mg, 0.53 mmol) was added at room temperature. After 5 minutes solvent was removed under reduced pressure. To the white residue, 10 mL 1.0 N HCl was added on an ice bath. The mixture was stirred for 15 min at 25 °C and extracted with CH_2Cl_2 (3x 20 mL). The combined organic phases were dried with Na_2SO_4 and chromatographed on silica gel using 1:1 hexanes:ethyl acetate as eluent to afford alcohol (+)-**53** (81 mg, 95%) as a white solid. ^1H NMR (500 MHz, acetone-d6): δ 9.53 (d, J=7.9 Hz, 1H), 8.11 (d, J=8.5 Hz, 1H), 7.88 (d, J=7.7 Hz, 1H), 7.51 (d, J=8.2 Hz, 1H), 7.46 (app.t, J=7.2 Hz, 1H), 7.36 (app.t, J=7.9 Hz, 1H), 7.29 (app.t, J=7.4 Hz, 1H), 7.22 (app.t, J=7.4 Hz, 1H), 7.08 (s, 1H), 6.98 (d, J=8.3 Hz, 1H), 6.91 (d, J=8.2 Hz, 1H), 6.76 (d, J=5.1 Hz, 1H), 4.95 (d, J=17.1 Hz, 1H), 4.90 (d, J=71.1 Hz, 1H), 4.89 (d, J=15.2 Hz, 1H), 4.85 (d, J=15.2 Hz, 1H), 4.24 (d, J=.85 Hz, 1H), 4.23 (bs, 1H), 4.14 (d, J=8.6 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.64 (bs, 1H), 2.76 (d, J=15.1 Hz, 1H), 2.65 (d, J=15.1 Hz, 1H), 2.35 (s, 3H). ^{13}C NMR (125 MHz, acetone-d6): δ 170.4, 150.6, 149.7, 141.2, 137.7, 132.0, 130.7, 130.4, 127.6, 127.1, 125.8, 125.3, 125.0, 124.3, 121.5, 121.0, 120.6, 120.0, 119.8, 116.6, 116.0, 115.0, 112.8, 108.9, 93.3, 80.6, 74.7, 65.4, 56.1, 50.4, 46.6, 35.4, 30.4. IR (thin film/NaCl): 3355.5 (brm), 2922.9 (m), 2847.8 (m), 1654.5 (s), 1501.5 (w), 1449.3 (s), 1254.5 (s), 1136.8 (s), 1025.7 (m), 747.1 (s) cm^{-1}. $[\alpha]_D^{25}$ +37° (c=0.1, MeOH).

Preparation of methyl ether (+)-**54** To a stirred suspension of NaH (14 mg, 0.58 mmol) in THF (1.0 mL) was added a solution of alcohol (+)-**53** (81 mg, 0.138 mmol) in THF (7 mL). The resulting mixture was stirred for 10 min with the visible evolution of gas, and for an additional 15 min thereafter. Addition of MeI (9.5 μL, 0.15 mmol) produced a single product by TLC (2.5:1 hexanes:acetone). After approximately 50 min the reaction was quenched by addition of 1.0 mL 1.0N HCl followed by 2.0 mL H_2O. Extraction of the solution with CH_2Cl_2 (3x 10 mL), drying over Na_2SO_4 and evaporation to a residue which could be purified by MPLC (2.5:1 hexanes:acetone) provided methyl ether (+)-**54** (67 mg, 80%) as a yellow foam. ^1H NMR (500 MHz, $CDCl_3$): δ 9.54 (d, J=7.9 Hz, 1H), 7.90 (d, J=8.5 Hz, 1H), 7.81 (d, J=7.7 Hz, 1H), 7.48 (app.t, J=7.6 Hz, 1H), 7.41 (app.t, J=7.2 Hz, 1H), 7.38 (app.t, J=7.2 Hz, 1H), 7.28 (m, 2H), 6.97 (d, J=8.2 Hz, 1H), 6.95 (s, 1H), 6.86 (d, J=8.1 Hz, 1H), 6.60 (d, J=5.8 Hz, 1H), 4.96 (d, J=15.0 Hz, 1H), 4.89 (d, J=15.0 Hz, 1H), 4.84 (d, J=16.7 Hz, 1H), 4.79 (d, J=16.6 Hz, 1H), 4.38 (d, J=2.6 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.71 (d, J=2.6 Hz, 1H), 3.57 (s, 3H), 2.76 (dd, J=3.1, 15.1 Hz, 1H), 2.50 (bd, J=14.7 Hz, 1H), 2.3 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, 315 K): δ 170.3, 149.6, 148.7, 140.1, 136.8, 130.8, 129.4, 127.0, 126.4, 125.3, 124.8, 124.3, 123.7, 120.7, 120.4, 120.2, 120.0, 119.6, 116.0, 115.5, 114.5, 111.6, 111.5, 107.1, 90.7, 83.2, 79.5, 60.6, 57.4, 56.1, 56.0, 49.9, 46.5, 33.6, 30.1. IR (thin film/NaCl): 3423.7 (brm), 2923.2 (s), 2848.1 (m), 2636.2 (m), 1647.2 (s), 1514.3 (m), 1462.9 (s), 1258.0 (m), 1235.3 (m), 1136.9 (m), 1026.9 (w), 743.3 (s) cm^{-1}. $[\alpha]_D^{25}$ +48° (c=0.1, MeOH).

Preparation of (+)-RK-286c (**50**) To a stirred solution of ether (+)-**54** (10 mg, 0.017 mmol) in anisole or thioanisole (80 μL, ≈50 equiv) was added TFA (0.5 mL). The reaction was monitored by TLC, and after 24 h had proceeded to completion, whereupon 1.0 mL H_2O was added, followed by extraction with CH_2Cl_2 (3x 5mL). Combined organic layers were washed with saturated aqueous $NaHCO_3$ (5 mL), dried over Na_2SO_4, and evaporated to a residue, which was purified by preparative TLC (5% MeOH:CH_2Cl_2) to provide (+)-RK-286c (**50**, 6 mg, 75%). ^1H NMR (500 MHz, DMSO-d_6): δ 9.27 (d, J=7.9 Hz, 1H), 8.47 (bs, 1H), 7.99 (d, J=8.5 Hz, 1H), 7.94 (d, J=7.7 Hz, 1H), 7.59 (d, J=8.2 Hz, 1H), 7.45 (app.t, J=7.4 Hz, 1H), 7.40 (app.t, J=7.5 Hz, 1H), 7.26 (app.t, J=7.5 Hz, 1H), 6.78 (d, J=5.3

Hz, 1H), 4.95 (d, J=17.6 Hz, 1H), 4.89 (d, J=17.7 Hz, 1H), 4.25 (bs, 1H), 4.17 (bs, 1H), 3.83 (d, J=2.7 Hz, 1H), 3.41 (s, 3H), 2.60 (ddd, J=3.2, 5.6, 14.8 Hz, 1H), 2.41 (dd, J=3.3, 14.8 Hz, 1H), 2.31 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 139.7, 136.1, 129.5, 125.5, 124.7, 124.1, 123.9, 122.6, 120.6, 119.5, 118.9, 118.6, 115.7, 108.6, 90.9, 82.3, 79.5, 58.8, 56.4, 45.3, 33.9, 29.9. IR (thin film/NaCl): 3354.0 (brm), 2920.4 (s), 2851.6 (m), 1677.2 (s), 1636.0 (m), 1585.3 (m), 1456.2 (s), 1352.8 (s), 1318.7 (s), 1231.7 (m), 1117.3 (m), 743.8 (s) cm^{-1}. $[\alpha]_D^{25}$ +41.1° (c=0.18, EtOAc); natural RK-286c $[\alpha]_D^{20}$ +45.3° (c=0.22, EtOAc).

Preparation of Diol (+)-**55** To a stirred solution of ether (+)-**54** (112 mg, 0.186 mmol) in $CDCl_3$ (2.0 mL) was added Martin's sulfurane (187 mg, 0.28 mmol). The reaction rapidly proceeded to a less polar product as monitored by TLC, and after 20 min was complete. Solvent was evaporated and the reidue subjected to silica gel chromatography (2:1 hexanes:ethyl acetate) to provide an olefin (96 mg, 88%) as a white solid. ^1H NMR (500 MHz, DMSO-d_6, 315 K): δ 9.31 (d, J=7.9 Hz, 1H), 8.11 (d, J=8.6 Hz, 1H), 7.91 (d, J=7.7 Hz, 1H), 7.86 (d, J=8.2 Hz, 1H), 7.50 (td, J=1.0, 7.34 Hz, 1H), 7.43 (app.t, J=7.8 Hz, 1H), 7.31 (app.t, J=7.0 Hz, 1H), 7.28 (app.t, J=7.1 Hz, 1H), 7.13 (d, J=1.9 Hz, 1H), 7.02 (s, 1H), 6.93 (d, J=8.6 Hz, 1H), 6.92 (d, J=8.6 Hz, 1H), 6.09 (d, J=10.4 Hz, 1H), 5.77 (dt, J=2.3, 10.4 Hz, 1H), 4.95 (s, 2H), 4.85 (d, J=15.1 Hz, 1H), 4.81 (d, J=15.1 Hz, 1H), 4.48 (d, J=1.4 Hz, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 3.57 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (125 MHz, acetone-d_6): δ 169.9, 150.5, 149.7, 141.3, 137.4, 131.8, 131.2, 130.5, 127.7, 127.1, 126.4, 126.2, 125.5, 125.3, 124.3, 121.5, 121.2, 121.1, 120.5, 120.4, 118.0, 117.1, 115.9, 112.8, 112.8, 109.1, 91.5, 80.8, 78.8, 57.7, 56.0, 56.0, 50.5, 46.5, 28.0. IR (thin film/NaCl): 2920.5 (s), 2851.5 (s), 1709.8 (m), 1674.3 (s), 1589.0 (m), 1513.7 (m), 1457.5 (s), 1222.9 (m), 1026.6 (m), 745.3 (m) cm^{-1}. $[\alpha]_D^{25}$ +36° (c=0.1, MeOH). To a stirred solution of 4-methylmorpholine N-oxide (6 mg, 0.05 mmol) and OsO_4 (0.6 mL of a 2.5% solution in *t*-BuOH, 0.05 mmol) in 4:1 acetone:H_2O (2 mL) was added solution of the olefin (25 mg, 0.043 mmol) in acetone (1 mL). The reaction was monitored by TLC, and after 16 h had proceeded to completion, whereupon 100 mg $NaHSO_3$ was added in 1.0 mL H_2O, and the black solution was stirred for 20 min and filtered, followed by extraction with CH_2Cl_2 (3x 15mL). Combined organic layers were dried over Na_2SO_4, and evaporated to a residue, which was purified by MPLC (1:1 hexanes:ethyl

acetate) to provide diol (+)-**55** (23 mg, 84%) as a white powder. ^{1}H NMR (500 MHz, DMSO-d$_6$): δ 9.36 (d, J=7.9 Hz, 1H), 7.95 (d, J=8.6 Hz, 1H), 7.94 (d, J=7.6 Hz, 1H), 7.64 (d, J=8.1 Hz, 1H), 7.55 (app.t, J=7.6 Hz, 1H), 7.45 (app.t, J=7.7 Hz, 1H), 7.35 (app.t, J=7.5 Hz, 1H), 7.29 (app.t, J=7.5 Hz, 1H), 7.02 (s, 1H), 6.94 (s, 2H), 6.59 (d, J=1.6 Hz, 1H), 6.13 (d, J=3.8 Hz, 1H), 5.07 (d, J=6.0 Hz, 1H), 4.99 (d, J=17.8 Hz, 1H), 4.95 (d, J=17.8 Hz, 1H), 4.83 (s, 2H), 4.12 (d, J=10.1 Hz, 1H), 4.12 (dd, J=2.3, 3.8 Hz, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 3.62 (s, 3H), 3.55 (ddd, J=2.3, 6.1, 10.1 Hz, 1H), 2.37 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d$_6$): δ 168.8, 148.9, 148.1, 140.3, 136.5, 130.4, 129.9, 127.8, 125.7, 125.0, 124.7, 123.5, 122.7, 120.8, 120.2, 119.9, 119.9, 118.7, 115.5, 114.8, 114.1, 112.0, 111.7, 108.8, 95.6, 87.3, 83.1, 71.7, 65.6, 61.6, 55.5, 55.5, 49.6, 45.5, 29.0. IR (thin film/NaCl): 3411.2 (brm), 2929.3 (m), 2849.4 (w), 2656.3 (m), 1590.0 (m), 1514.0 (m), 1461.2 (s), 1350.9 (m), 1273.6 (s), 1127.1 (s), 1025.0 (m), 743.3 (s) cm^{-1}. $[\alpha]_D^{25}$ +17° (c=0.1, MeOH).

Preparation of (+)-MLR-52 (**51**) To a stirred solution of diol (+)-**55** (10 mg, 0.016 mmol) in anisole or thioanisole (80 μL, ≈50 equiv) was added TFA (0.5 mL). The reaction was monitored by TLC, and after 16 h had proceeded to completion, whereupon 1.0 mL H$_2$O was added, followed by extraction with CH_2Cl_2 (3x 5mL). Combined organic layers were washed with saturated aqueous $NaHCO_3$ (5 mL), dried over Na_2SO_4, and evaporated to a residue, which was purified by preparative TLC (5% MeOH:CH_2Cl_2) to provide (+)-MLR-52 (**51**, 6 mg, 77%). ^{1}H NMR (500 MHz, DMSO-d$_6$): δ 9.31 (d, J=7.9 Hz, 1H), 8.61 (bs, 1H), 7.99 (d, J=7.7 Hz, 1H), 7.96 (d, J=8.7 Hz, 1H), 7.62 (d, J=8.2 Hz, 1H), 7.53 (app.t, J=7.5 Hz, 1H), 7.45 (td, J=0.8, 7.7 Hz, 1H), 7.32 (app.t, J=7.4 Hz, 1H), 7.32 (app.t, J=7.4 Hz, 1H), 6.58 (d, J=1.6 Hz, 1H), 6.12 (d, J=4.0 Hz, 1H), 5.06 (d, J=5.9 Hz, 1H), 4.99 (d, J=17.6 Hz, 1H), 4.95 (d, J=17.5 Hz, 1H), 4.13 (d, J=10.3 Hz, 1H), 4.12 (dd, J=1.6, 2.6 Hz, 1H), 3.62 (s, 3H), 3.56 (ddd, J=2.6, 6.2, 10.3 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d$_6$): δ 171.8, 140.2, 136.4, 132.6, 127.8, 125.8, 125.5, 124.8, 124.6, 123.6, 122.7, 120.9, 120.1, 119.7, 119.3, 115.4, 114.9, 114.3, 108.7, 95.6, 87.2, 83.1, 71.7, 65.6, 61.6, 45.4, 29.0. IR (thin film/NaCl): 3348.5 (brm), 2922.9 (s), 2851.9 (m), 1638.2 (s), 1586.6 (m), 1455.5 (s), 1373.5 (m), 1336.6 (m), 1320.8 (m), 1275.0 (m), 1224.7 (m), 1200.3 (w), 1119.5 (s), 740.8 (s,) cm^{-1}. $[\alpha]_D^{25}$ +65° (c=0.1, MeOH); natural MLR-52 $[\alpha]_D$ +68° (c=0.093, MeOH).

Preparation of oxime (-)-**56** A suspension of ketone (+)-**51** (100 mg, 0.17 mmol), hydroxylamine hydrochloride (165 mg, 2.38 mmol), and NaOAc (167 mg, 2.04 mmol) in 80% aqueous EtOH (35.0 mL) was heated gently to reflux for 30 min. Following cooling to room temperature, sovent was removed *in vacuo*, and the residue purified by MPLC (1:1 hexanes:ethyl acetate) to provide oxime (-)-**56** (98 mg, 95%) as a yellow powder. ^{1}H NMR (500 MHz, DMSO-d6): δ 10.3 (s, 1H), 9.34 (d, J=7.9 Hz, 1H), 8.08 (d, J=8.6 Hz, 1H), 7.90 (d, J=7.6 Hz, 1H), 7.71 (d, J=8.3 Hz, 1H), 7.51 (app.t, J=7.6 Hz, 1H), 7.42 (app.t, J=7.9 Hz, 1H), 7.32 (app.t, J=7.7 Hz, 1H), 7.28 (app.t, J=7.4 Hz, 1H), 7.04 (d, J=6.3 Hz, 1H), 7.03 (s, 1H), 6.95 (d, J=8.4 Hz, 1H), 6.93 (d, J=8.2 Hz, 1H), 5.56 (m, 2H), 4.97 (d, J=18.1 Hz, 1H), 4.93 (d, J=16.9 Hz, 1H), 4.85 (d, J=15.0 Hz, 1H), 4.45 (d, J=15.0 Hz, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 3.61 (d, J=13.9 Hz, 1H), 3.01 (dd, J=5.8, 14.3 Hz, 1H), 2.46 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d6): δ 168.8, 148.9, 148.1, 147.4, 140.2, 136.1, 130.5, 129.6, 128.1, 125.4, 125.3, 124.7, 124.6, 123.6, 122.8, 120.5, 120.1, 119.9, 119.6, 118.5, 116.0, 114.8, 113.9, 112.1, 111.9, 108.9, 97.4, 82.0, 74.9, 55.5, 55.5, 49.5, 45.5, 29.6, 28.6. IR (thin film/NaCl): 3324.0 (brm), 2995.0 (w), 2911.3 (m), 1660.0 (s), 1589.7 (m), 1513.5 (s), 1461.1 (s), 1417.9 (m), 1399.0 (m), 1349.2 (s), 1315.5 (m), 1260.0 (s), 1234.6 (m), 1124.4 (m), 1027.2 (m), 741.7 (s) cm^{-1}. $[\alpha]_D^{20}$ -18° (c=0.1, CH_2Cl_2).

Preparation of methoxy oxime (-)-**57** To a mixture of oxime (-)-**56** (90 mg, 0.15 mmol), MeI (88μL, 1.42 mmol), and powdered KOH (88 mg, 1.58 mmol) was added *n*-Bu4NBr (10 mg, 0.03 mmol). The mixture was stirred under N_2 for 30 min, solvent was removed *in vacuo*, and the residue was subjected to silica gel chromatography (1:1 hexanes:ethyl acetate) to provide methoxime (-)-**57** (85 mg, 90%) as a yellow powder. ^{1}H NMR (500 MHz, DMSO-d6, 345 K): δ 9.36 (d, J=8.0 Hz, 1H), 7.99 (d, J=8.6 Hz, 1H), 7.93 (d, J=7.8 Hz, 1H), 7.68 (d, J=8.3 Hz, 1H), 7.51 (app.t, J=7.6 Hz, 1H), 7.44 (app.t, J=7.8 Hz, 1H), 7.33 (app.t, J=7.2 Hz, 1H), 7.30 (app.t, J=7.1 Hz, 1H), 7.04 (s, 1H), 7.02 (d, J=5.6 Hz, 1H), 6.97 (d, J=9.4 Hz, 1H), 6.94 (d, J=8.1 Hz, 1H), 4.97 (s, 2H), 4.86 (d, J=15.5 Hz, 1H), 4.85 (d, J=15.7 Hz, 1H), 4.76 (s, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.54 (d, J=14.4 Hz, 1H), 3.45 (s, 3H), 3.16 (dd, J=5.9, 14.4 Hz, 1H), 3.14 (s, 3H), 2.46 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d6): δ 168.7, 148.9, 148.1, 147.3, 139.8, 136.1, 130.4,

129.5, 128.0, 125.4, 125.3, 124.7, 124.6, 123.6, 122.7, 120.6, 120.2, 119.9, 119.6, 118.6, 115.5, 114.9, 113.8, 112.2, 112.0, 108.9, 96.1, 83.3, 82.0, 60.8, 58.4, 55.5, 55.5, 49.5, 45.4, 30.4, 28.5. IR (thin film/NaCl): 2998.0 (w), 2926.3 (m), 1674.1 (s), 1590.0 (m), 1513.7 (s), 1460.9 (s), 1418.2 (m), 1397.9 (s), 1349.4 (s), 1316.2 (s), 1262.1 (m), 1225.6 (m), 1044.3 (m), 743.5 (m) cm^{-1}. $[\alpha]_D^{25}$ -22° (c=0.1, CH_2Cl_2).

Preparation of amine (+)-**58** A mixture of oxime (+)-**57** (85 mg, 0.13 mmol) and PtO_2 (28 mg) in a 60% aqueous acetic acid (15.0 mL) was treated with H_2, and the reaction was monitored by TLC (1:1 hexanes:ethyl acetate). Upon completion, the mixture was filtered through celite and the filtrate was evaporated. The residue was dissolved in CH_2Cl_2 (40 mL) and washed with 8.0 mL 1.0N NaOH. The aqueous layer was then back-extracted with CH_2Cl_2 (2x 15 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to a residue (79 mg), which was used in the next step without further purification. An analitical sample of primary amine (+)-**58** could be obtained by preparative TLC of the above residue using 5% MeOH:CH_2Cl_2 as eluent. ^1H NMR (500 MHz, $CDCl_3$, 310 K): δ 9.55 (d, J=7.9 Hz, 1H), 7.95 (d, J=8.5 Hz, 1H), 7.83 (d, J=7.7 Hz, 1H), 7.51 (app.t, J=7.6 Hz, 1H), 7.42 (app.t, J=8.2 Hz, 1H), 7.40 (app.t, J=7.5 Hz, 1H), 7.30 (app.t, J=7.8 Hz, 2H), 6.99 (d, J=9.4 Hz, 2H), 6.87 (d, J=8.0 Hz, 1H), 6.59 (d, J=4.9 Hz, 1H), 4.98 (d, J=14.9 Hz, 1H), 4.92 (d, J=14.9 Hz, 1H), 4.87 (d, J=16.7 Hz, 1H), 4.82 (d, J=16.7 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.75 (m, 2H), 3.46 (s, 3H), 2.63 (m, 2H), 2.32 (s, 3H), 1.27 (bs, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, 315 K): δ 170.2, 149.6, 148.7, 140.1, 137.0, 130.8, 129.6, 129.5, 127.0, 126.2, 125.4, 124.7, 124.5, 123.8, 120.8, 120.5, 120.2, 120.2, 119.6, 116.0, 115.4, 114.6, 111.6, 111.6, 107.4, 91.3, 84.2, 80.2, 57.5, 56.1, 56.1, 49.9, 46.5, 42.6, 34.6, 30.0. IR (thin film/NaCl): 3414.7 (brw), 2920.8 (s), 2851.7 (s), 1733.7 (w), 1672.8 (s), 1636.0 (w), 1588.1 (m), 1513.5 (s), 1352.7 (s), 1259.3 (s), 1136.7 (m), 744.2 (m) cm^{-1}. $[\alpha]_D^{25}$ +14.3° (c=0.14, $CHCl_3$).

Preparation of (+)-staurosporine (**49**) Crude amine (+)-**58** was dissolved in THF (2.0 mL) and treated with formic acetic anhydride in THF (1.3 μL of a 1.3 M solution in THF, 0.17 mmol)(FAA prepared by treatment of 1.0 equiv acetic anhydride with 1.2 equiv formic acid followed by reflux for 2 h). TLC analysis showed rapid formation of a less polar substance. A stream of N_2

was used to evaporate the solvent, followed by high vacuum for 15 min. THF (1.3 mL) was added to dissolv the residue, the reaction vessel was cooled to 0 °C, and BH_3•DMS (193 μL of a 2.0 N solution in toluene, 0.39 mmol) was introduced. The solution was heated to reflux for 2 h at which point it was again cooled to 0 °C. Methanolic HCl (1.0 mL) was added along with excess MeOH (1.3 mL) and the solution was refluxed for an additional hour. Following cooling, volitiles were removed *in vacuo*, and the solid residue was azeotroped with MeOH (5x 5.0 mL). To the remaining residue was added 7.0 mL CH_2Cl_2 followed by 1.0 N NaOH (5.0 mL), layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3x 7.0 mL). Combined organic layers were dried over Na_2SO_4, evaporated, and purified by MPLC (5% MeOH:CH_2Cl_2) to give a methyl amine (80 mg, 91% 2 steps from 14) as a yellow foam. ^1H NMR (500 MHz, $CDCl_3$, 320 °K): δ 9.55 (d, J=7.9 Hz, 1H), 7.89 (d, J=8.5 Hz, 1H), 7.82 (d, J=7.3 Hz, 1H), 7.48 (td, J=1.0, 7.5 Hz, 1H), 7.39 (td, J=1.0, 7.4 Hz, 1H), 7.38 (app.t, J=7.3 Hz, 1H), 7.27 (m, 2H), 7.01 (m, 2H), 6.88 (d, J=8.7 Hz, 1H), 6.57 (dd, J=1.4, 6.0 Hz, 1H), 4.98 (d, J=14.9 Hz, 1H), 4.91 (d, J=14.9 Hz, 1H), 4.84 (s, 2H), 3.92 (d, J=3.0 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.37 (dd, J=3.8, 7.7 Hz, 1H), 3.33 (bs, 3H), 2.72 (ddd, J=1.3, 4.6, 14.5 Hz, 1H), 2.46 (m, 1H), 2.35 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 149.3, 148.4, 139.6, 136.7, 130.6, 130.4, 129.3, 127.1, 126.6, 125.1, 124.5, 124.3, 123.5, 120.7, 120.4, 120.0, 119.8, 119.1, 115.5, 114.9, 114.0, 111.2, 111.2, 107.0, 91.2, 83.9, 80.2, 57.5, 56.0, 55.9, 50.7, 49.9, 46.4, 33.2, 30.1, 29.9. IR (thin film/NaCl): 2954.1 (m), 2915.1 (m), 1673.2 (s), 1635.8 (m), 1462.7 (s), 1399.0 (s), 1352.6 (s), 1258.7 (m), 1136.5 (m), 1026.9 (m), 745.2 (s) cm^{-1}. $[\alpha]_D^{25}$ +22° (c=0.1, MeOH).

To a stirred solution of the amine (10 mg, 0.016 mmol) in anisole or thioanisole (80 μL, ≈50 equiv) was added TFA (0.5 mL). The sluggish reaction was monitored by TLC, and after 48 h had proceeded to completion, whereupon 1.0 mL H_2O was added, and the solution was adjusted to pH10 with 5.0 N NaOH, followed by extraction with CH_2Cl_2 (3x 5mL). Combined organic layers were dried over Na_2SO_4, and evaporated to a residue, which was purified by preparative TLC (5% MeOH:CH_2Cl_2) to provide (+)-Staurosporine (**49**, 6 mg, 70%). ^1H NMR (500 MHz, $CDCl_3$): δ 9.43 (d, J=7.9 Hz, 1H), 7.94 (8.5, 1H), 7.90 (d, J=7.7 Hz, 1H), 7.49 (app.t, J=7.6 Hz, 1H), 7.43 (app.t, J=7.7 Hz, 1H), 7.37 (app.t, J=7.5 Hz, 1H), 7.33 (app.t, J=7.4 Hz, 1H), 7.30 (d, J=8.0 Hz, 1H), 6.57 (d, J=5.6 Hz, 1H), 6.33 (bs, 1H), 5.05 (d, J=15.8 Hz, 1H), 5.01 (d, J=15.8 Hz, 1H), 3.89 (bs, 1H),

3.42 (s, 3H), 3.37 (d, 3.2H), 2.76 (dd, J=3.9, 14.7 Hz, 1H), 2.41 (bd, J=15.4 Hz, 1H), 2.37 (s, 3H), 1.59 (bs, 1H), 1.57 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.6, 139.8, 136.7, 132.2, 130.8, 126.6, 125.0, 124.6, 124.2, 123.4, 120.6, 120.0, 119.8, 115.3, 114.1, 106.9, 91.1, 84.2, 80.1, 57.2, 50.4, 45.9, 33.3, 30.3, 30.1. IR (thin film/NaCl): 3316.6 (m), 2925.0 (m), 2850.8 (m), 1678.7 (s), 1636.2 (m), 1584.2 (m), 1457.5 (s), 1352.2 (s), 1316.7 (s), 1281.3 (m), 1115.5 (m), 744.8 (s) cm^{-1}. $[\alpha]_D^{25}$ +35° (c=0.1, MeOH); natural staurosporine $[\alpha]_D^{25}$ +35° (c=1.0, MeOH).

The above description is for the purpose of teaching the person of ordinary skill in the art how to practice the present invention, and it is not intended to detail all those obvious modifications and variations of it which will become apparent to the skilled worker upon reading the description. It is intended, however, that all such obvious modifications and variations be included within the scope of the present invention, which is defined by the following claims. The claims are intended to cover the claimed components and steps in any sequence which is effective to meet the objectives there intended, unless the context specifically indicates the contrary.

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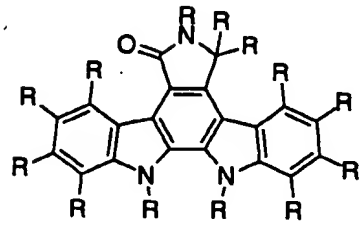
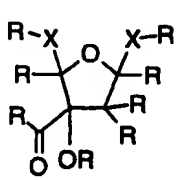
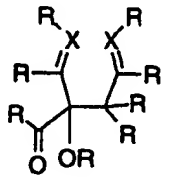
Claims

1. A process for the preparation of furanosylated indolocarbazoles of the formula

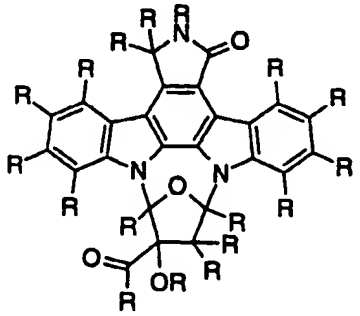


by reacting an acetal selected from the group consisting of the formulae





and mixtures thereof,
to produce a glycosylated product of the formula



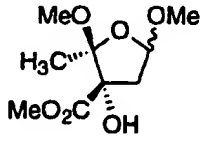
wherein R is selected from the group consisting of H, C, N, S, O, Cl, Br, I, Si, F, and mixtures thereof.

2. A process according to claim 1 wherein said preparation is carried out under conditions that promote acetal exchange or formation.

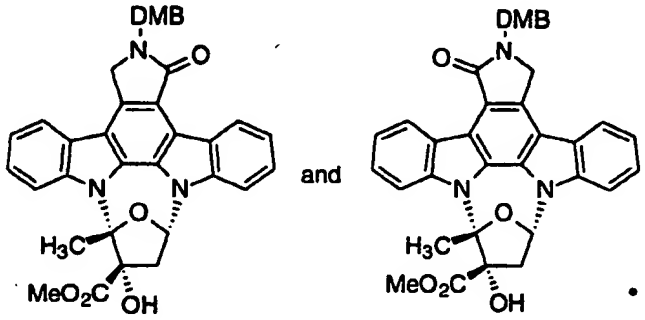
3. A process according to claim 2 wherein said preparation is carried out in the presence of a Bronsted acid or a Lewis acid.

4. A process according to claim 1 wherein camphor sulfonic acid is used as a catalyst and dichloroethane is used as a solvent.

5. A process according to claims 1 to 4 wherein a furanose of the formula

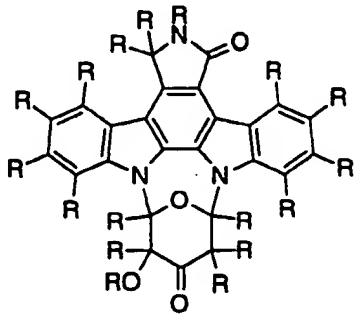


is reacted with DMB-protected K252c to give two products of the formulae

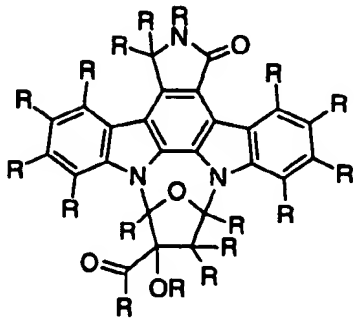


6. A product prepared according to the process of claims 1 to 5.

7. A process for the stereoselective preparation of pyranosylated indolocarbazoles of the formula



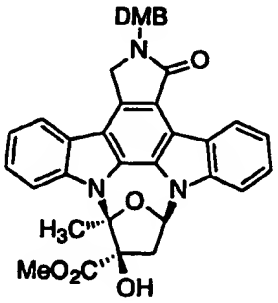
by ring expansion of the corresponding furanosylated indolocarbazole of the formula



wherein R is selected from the group consisting of H, C, N, S, O, Cl, Br, I, Si, F, and mixtures thereof.

8. A process according to claim 7 wherein the ring expansion is carried out in the presence of a Bronsted acid or a Lewis acid.

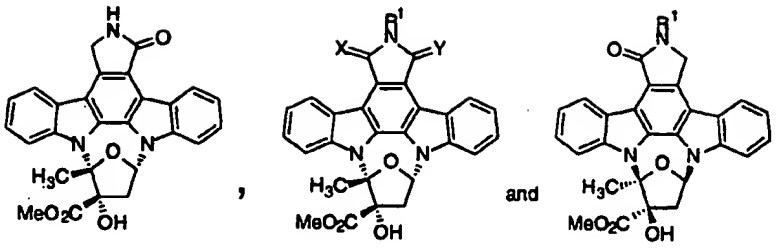
9. A process according to claims 7 or 8 wherein the ring expansion is carried out in a multistep procedure wherein a compound of the formula



is first reduced with $LiBH_4$, the derived diol is oxidized, and the resulting intermediate compound is then subjected to $BF_3 \bullet Et_2O$.

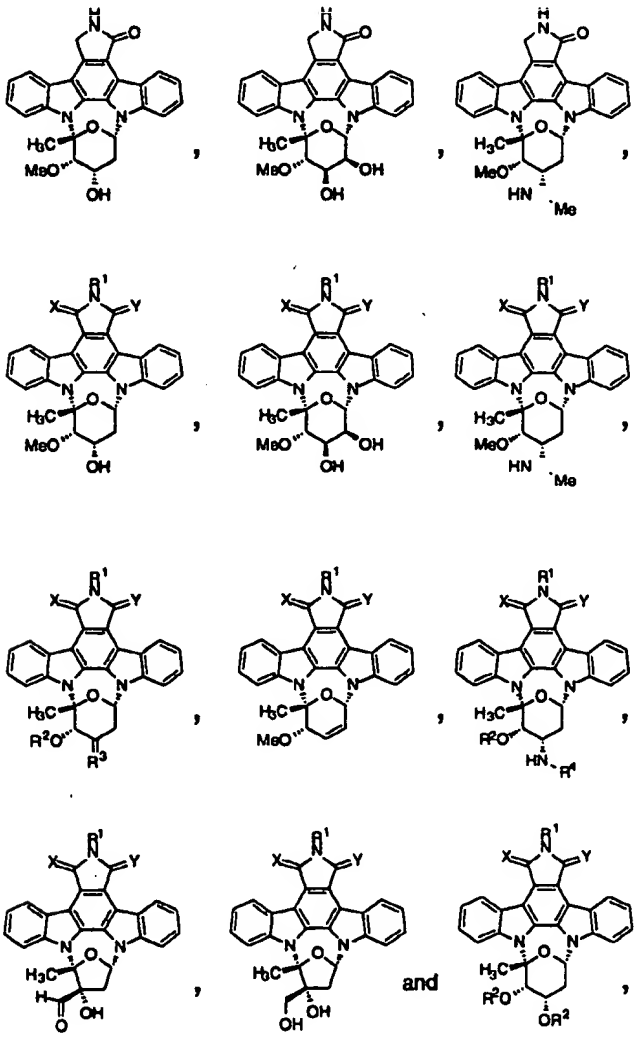
10. A product produced by the process of claims 7, 8, or 9.

11. A compound selected from the group consisting of



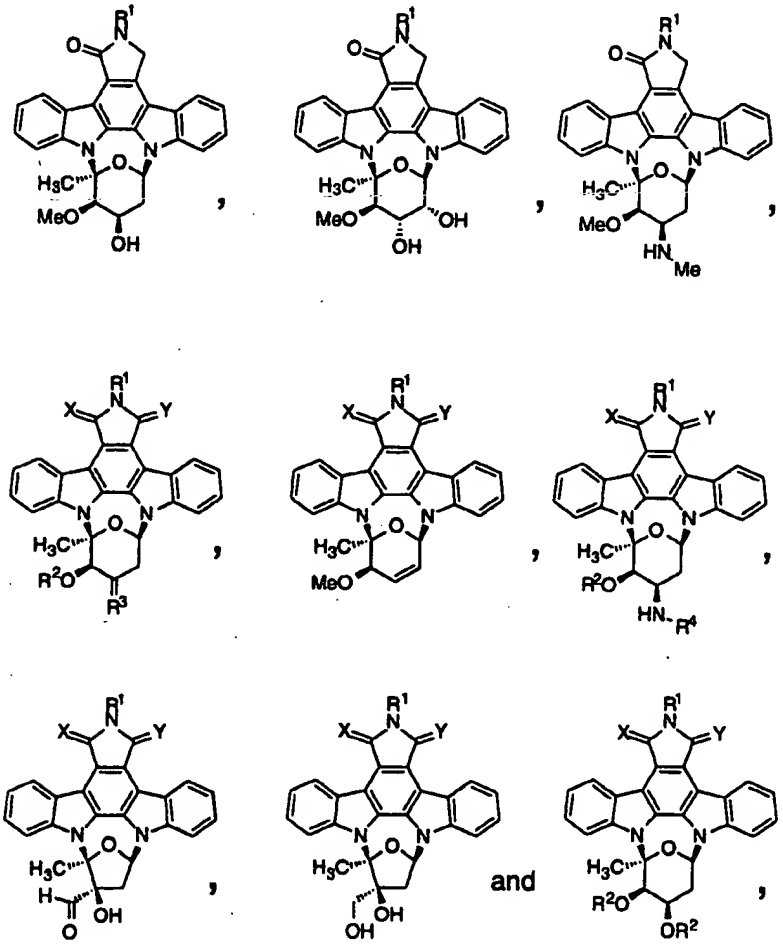
wherein R^1 is selected from the group consisting of H, *t*-Bu, 3,4-dimethoxybenzyl, 4-methoxybenzyl, benzyl, and X and Y are selected from the group consisting of O and H.

12. A compound selected from the group consisting of



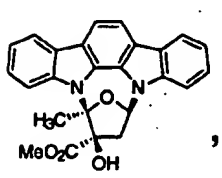
wh rein R^1 is selected from the group consisting of H, *t*-Bu, 3,4-dimethoxybenzyl, 4-methoxybenzyl, benzyl; R^2 is selected from the group consisting of, H and CH_3; R^3 is selected from the group consisting of O, NOH, and NOBn; R^4 is selected from the group consisting of H, CHO, and CH_3; and X and Y are selected from the group consisting of O and H.

13. A compound selected from the group consisting of



wherein R^1 is selected from the group consisting of, H, *t*-Bu, 3,4-dimethoxybenzyl, 4-methoxybenzyl, benzyl; R^2 is selected from the group consisting of H and CH_3; R^3 is selected from the group consisting of O, NOH, and NOBn; R^4 is selected from the group consisting of H, CHO, and CH_3; and X and Y are selected from the group consisting of O and H.

14. A compound s lected from the group consisting of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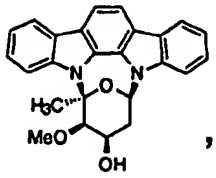
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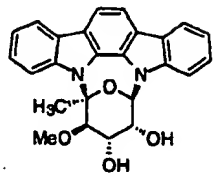
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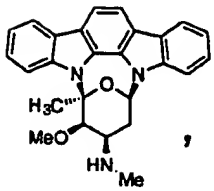
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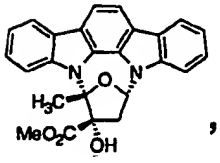
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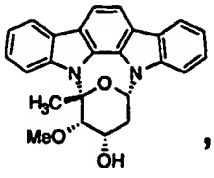
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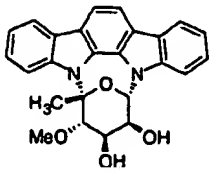
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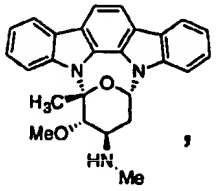
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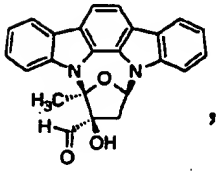
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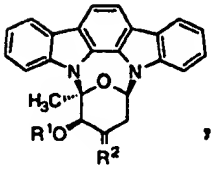
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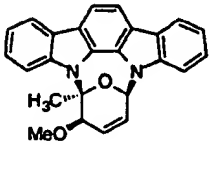
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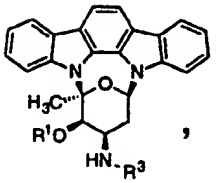
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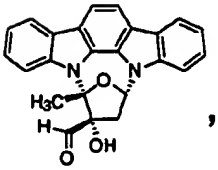
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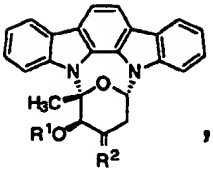
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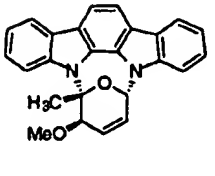
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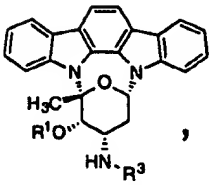
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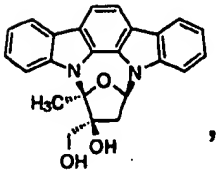
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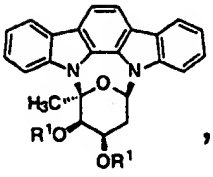
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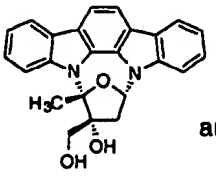
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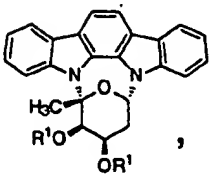
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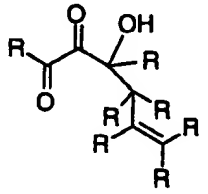
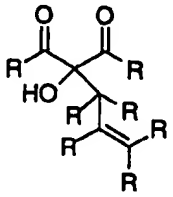
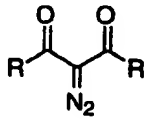
wherein R^1 is selected from the group consisting of H, CH_3; R^2 is selected from the group consisting of O, NOH, and NOBn; and R^3 is selected from the group consisting of H, CHO, and CH_3.

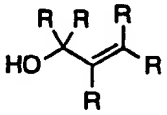
15. A process for preparing tertiary alcohols containing the structural features of compounds selected from the group consisting of


and


comprising reacting at least one diazo carbonyl compound of the formula



with an allylic alcohol of the formula,



wherein R is selected from the group consisting of H, C, N, S, O, Cl, Br, I, Si, F, and mixtures thereof,
under conditions that produce a carbene or carbenoid intermediate from the diazo compound and for a time sufficient to couple the compounds.

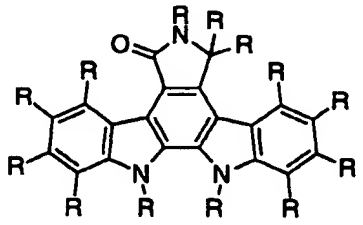
16. A process according to claim 15 wherein the reaction is promoted by thermolysis, photolysis, or a catalyst selected from the group consisting of transition metal catalysts, Bronsted acids, and Lewis acids.

17. A process according to claim 16 wherein the reaction is carried out in the presence of a transition metal catalyst.

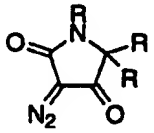
18. A process according to claim 17 wherein the catalyst is $Rh_2(OAc)_4$.

19. A product prepared according to the process of claims 15 to 18.

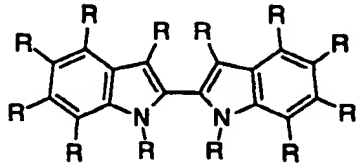
20. A process for the preparation of an indolocarbazole of the formula



comprising reacting a diazo compound of the formula



with a biindole of the formula



wherein R is selected from the group consisting of H, C, N, S, O, Cl, Br, I, Si, F, and mixtures thereof.

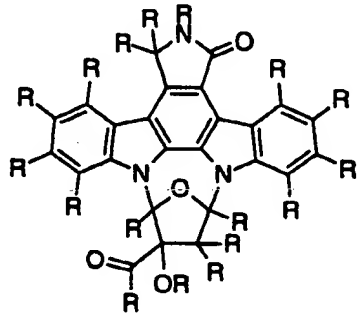
21. A process according to claim 20 wherein the reaction is carried out in the presence of a transition metal catalyst in a solvent capable of solvating the reactants.

22. A process according to claim 21 wherein the coupling reaction is carried out in the presence of a $Rh_2(OAc)_4$ catalyst.

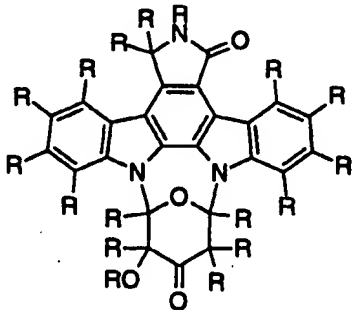
23. A process according to claims 20 to 22 wherein the diazo compound is a diazolaactam and the biindole is a 2,2'-biindole.

24. A product prepared according to the process of claims 20 to 23.

25. A process for the stereoselective preparation of a furanosylated indolocarbazole of the formula



by ring contraction of the corresponding pyranosylated indolocarbazole of the formula



wherein R is selected from the group consisting of H, C, N, S, O, Cl, Br, I, Si, F, and mixtures thereof.

26. A process according to claim 25 wherein the ring contraction is carried out in the presence of a compound capable of oxidizing an alcohol to a ketone and a reagent capable of effecting a benzilic acid-type rearrangement.

27. A process according to claims 25 or 26 wherein the ring contraction is a single-step procedure employing CuCl as both the oxidant and th rearrangement promoter, and methan l is used as a solvent.

28. A product prepared according to the process of claims 25, 26, or 27.